Temporal profile of central and peripheral neuromuscular features of acute Organophosphorus poisoning.

A prospective observational clinical study.

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE M.D. BRANCH I (GENERAL MEDICINE) EXAMINATION OF THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY, APRIL 2015

DECLARATION

I declare that this dissertation titled **'Temporal profile of central and peripheral neuromuscular features of acute Organophosphorus poisoning- A prospective observational clinical study'** has been conducted by me under the guidance and supervision of **Dr. (Prof) Anand Zachariah (MD.)**. It is submitted as a part of the fulfilment of requirement of the award of degree MD General Medicine for 2015 examination to be held under **The Tamil Nadu Dr. M.G.R. University**. I have not submitted this thesis for the award of any degree or diploma from any other university.

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CERTIFICATE

This is to certify that this research work titled **"Temporal profile of central and peripheral neuromuscular features of acute Organophosphorus poisoning-A prospective observational clinical study"** has been done by **Dr. Nirmalraj Francis**, MD general medicine Post Graduate trainee, Christian Medical College, Vellore, India.

Date:

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Principal,

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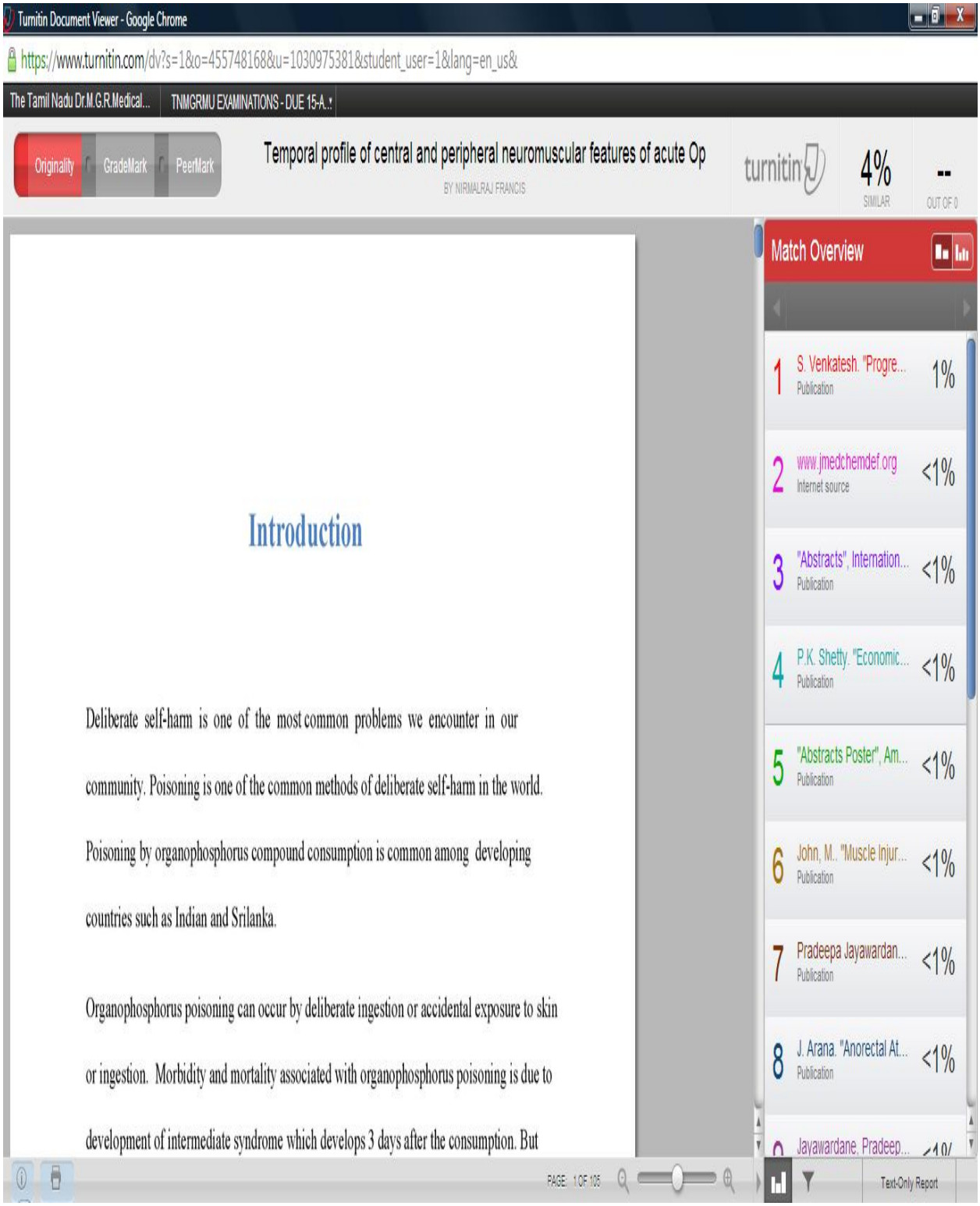

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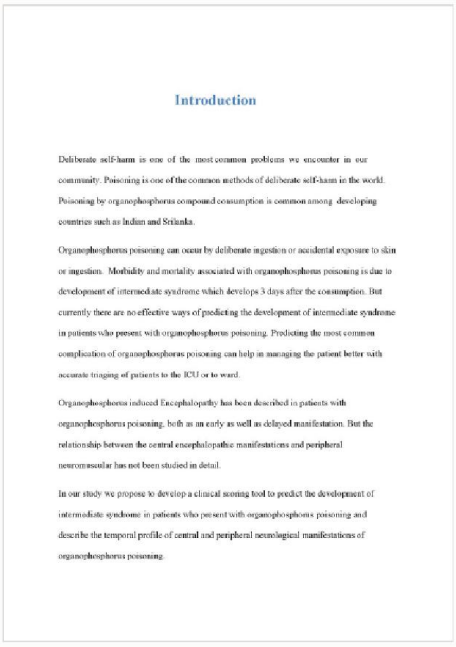

Introduction

Deliberate self-harm is one of the most common problems we encounter in our community. Poisoning is one of the common methods of deliberate self-harm in the world. Poisoning by organophosphorus compound consumption is common among developing countries such as Indian and Srilanka.

Organophosphorus poisoning can occur by deliberate ingestion or accidental exposure to skin or ingestion. Morbidity and mortality associated with organophosphorus poisoning is due to development of intermediate syndrome which develops 3 days after the consumption. But currently there are no effective ways of predicting the development of intermediate syndrome in patients who present with organophosphorus poisoning. Predicting the most common complication of organophosphorus poisoning can help in managing the patient better with accurate triaging of patients to the ICU or to ward.

Organophosphorus induced Encephalopathy has been described in patients with organophosphorus poisoning, both as an early as well as delayed manifestation. But the relationship between the central encephalopathic manifestations and peripheral neuromuscular has not been studied in detail.

In our study we propose to develop a clinical scoring tool to predict the development of intermediate syndrome in patients who present with organophosphorus poisoning and describe the temporal profile of central and peripheral neurological manifestations of organophosphorus poisoning.

ACKNOWLEDGMENTS

First of all I thank the Lord Almighty who has been my source of help and strength throughout my thesis work.

I am grateful to **Dr. Anand Zachariah,** Professor of medicine, my supervisor and guide, for his resourcefulness and scientific commitment. His continued support and encouragement was the key factor for this study to be completed successfully.

My sincere thanks to Dr. Jeyaseelan and Mrs Kavitha for helping me in the data analysis.

I would like thank all my teachers, colleagues and friends for constantly guiding me through the study.

Last, but not the least, I would like to thank my parents for their continuous support throughout the study.

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Scoring system to predict the development of Intermediate syndrome in patients with acute organophosphorous poisoning.
Dr. Nirmal Raj Francis, PG Registrar, General Medicine, Dr. Anand Zachariah, Medicine, Dr. Lovely Thomas, Dr. John Victor Peter, Medical ICU, Dr. Mathew Alexander, Neurological sciences, Dr. L. Jeyaseelan, Ms. Kavitha, Biostatistics, Dr. Thomas Isiah Sudarsanam, Dr. K.P.P Abhilash, Dr. Nathaniel Samson, Medicine.

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Dear Dr. Nirmal Raj Francis,

I enclose the following documents:-

1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Nihal Thomas, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr Nihal Thomas
MBBS MD MNAMS DNB (Endo) FRACP(Endo) FRCP(Edin)
Secretary (Ethics Committee)
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CC: Dr. Anand Zachariah, Department of Medicine, CMC.

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Dear Dr. Nirmal Raj Francis,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "Scoring system to predict the development of Intermediate syndrome in patients with acute organophosphorous poisoning." on April 16, 2013.

The Committees reviewed the following documents:

1. Format for application to IRB submission
2. Proforma
3. Patient information Sheet And Consent Form (English, Tamil and Telugu)

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4. Cvs of Drs. Nirmal Raj Francis, Anand Zachariah, Mathew Alexander, K.P.P Abhilash.
5. A CD containing document 1 – 5

The following Institutional Review Board (Research & Ethics Committee) members were present at the meeting held on April 16, 2013 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

Name	Qualification	Designation	Other Affiliations
Dr. Benjamin Perakath	MBBS, MS, FRCS	Professor, Surgery (Colorectal), CMC.	Internal, Clinician
Dr. T. Balamugesh	MBBS, MD(Int Med), DM, FCCP (USA)	Professor, Dept. of Pulmonary Medicine, CMC.	Internal, Clinician
Dr. Anup Ramachandran	Ph D	The Wellcome Trust Research Laboratory Gastrointestinal Sciences	Internal
Dr. Ellen Ebenezer Benjamin	M Sc	Maternity Nursing, CMC	Internal, Nurse
Dr. Denny Fleming	B Sc (Hons), PhD	Honorary Professor, Clinical Pharmacology, CMC.	Internal, Pharmacologist
Dr. Srinivas Babu	M Sc, Ph.D.	Sr. Scientist, Neurological Sciences, CMC.	Internal
Dr. Mathew Joseph	MBBS, MCH	Professor, Neurosurgery, CMC	Internal, Clinician
Mrs. Pattabiraman	B Sc, DSSA	Social Worker, Vellore	External, Lay Person
Mr. Sampath	B Sc, BL	Advocate	External, Legal Expert

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Additional Vice Principal (Research)

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Dr. Priya Abraham	MBBS, MD, PhD	Professor, Virology, CMC	Internal, Clinician
Dr Ashok Chacko	MD, DM, FRCP, FRCPG, FIMSA, FAMS	Director, Institute of Gastroenterology and Liver Disease, Madras Medical Mission, Chennai	External, Clinician
Dr. Bobby John	MBBS, MD, DM, PHD, MAMS	Cardiology, CMC	Internal, Clinician
Dr. Nihal Thomas	MD MNAMS DNB(Endo) FRACP(Endo) FRCP(Edin)	Secretary IRB (EC) & Dy. Chairperson (IRB), Profess Endocrinology& Addl. Vice Principal (Research), CMC.	Internal, Clinician

We approve the project to be conducted as presented.

The Institutional Ethics Committee expects to be informed about the progress of the project, any **adverse events** occurring in the course of the project, any **amendments in the protocol and the patient information / informed consent**. On completion of the study you are expected to submit a copy of the **final report**. Respective forms can be downloaded from the following link: http://172.16.11.136/Research/IRB_Polices.html in the CMC Intranet and in the CMC website link address: http://www.cmch-vellore.edu/static/research/Index.html.

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Fluid Grant Allocation:

A sum of Rs. 80,000/- (Rupees Eighty Thousand only will be granted for 2 years. A sum of Rs 40,000/- will be sanctioned for 12 months after receipt of the revised proposal, subsequent installment of 40,000/- each will be released at the end of the first year following the receipt of the progress report.

Yours sincerely

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr Nihal Thomas
MBBS MD MNAMS DNB (Endo) FRACP(Endo) FRCP(Edin)
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CONTENTS

Introduction

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In our study we propose to develop a clinical scoring tool to predict the development of intermediate syndrome in patients who present with organophosphorus poisoning and describe the temporal profile of central and peripheral neurological manifestations of organophosphorus poisoning.

Aims

And

Objectives

AIMS

To describe and correlate the central (encephalopathic) and peripheral neuromuscular features (Type 1 and Type II [Intermediate syndrome]) and their temporal profile in acute organophosphorus poisoning.

OBJECTIVES

1. To assess the utility of a clinical scoring system at admission to predict the development of Intermediate syndrome in patients with acute Organophosphorus poisoning.

2. To describe and correlate the central (encephalopathic) and peripheral neuromuscular features (Type 1 and Type II [Intermediate syndrome]) and their temporal profile in acute Organophosphorus poisoning.

Review

of

Literature

REVIEW OF LITERATURE

Deliberate self-harm is one the common problems in community. Suicide by consumption of poison is a common practice especially in developing countries and more than half the suicides in the world occur in India and China(1).

Pesticide poisoning due to organophosphorus compound consumption is a common method of suicide in southern India and Sri Lanka. In our institution Organophosphorus poisoning accounted for 12% of all intensive care admission and 70 % all admissions with a case fatality rate of 22 %.(2).

CHEMICAL COMPOSITION OF ORGANOPHOSPHORUS COMPOUND

All organophosphorus compounds have a similar chemical composition. They contain a central phosphorous atom attached to either a sulphur or oxygen by a double bond. All organophosphorous compound contains either a methyl or ethyl group along with a leaving group which is specific to every organophosphorous compound(3).

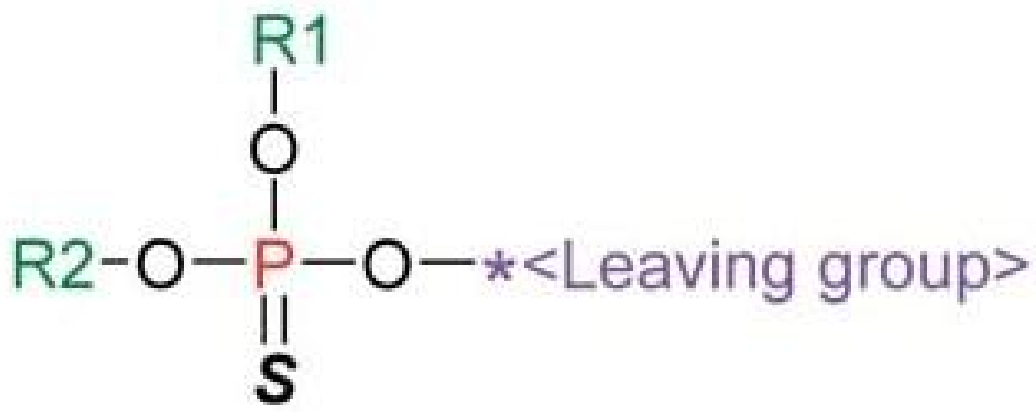


Figure 1 Chemical structure of OP compounds

MECHANISM OF ACTION OF ORGANOPHOSPHOROUS COMPOUND

Organophosphorus compound act by inhibiting carboxy ester hydrolases like acetylcholinesterase (AChE) enzyme by binding to the active site of the enzyme(4). AChE acts by splitting acetylcholine in the neuromuscular junction.

Acetyl cholinesterase is present in almost all living animals, vertebrates and invertebrates and is responsible for nervous conduction in organs and glands supplied by the parasympathetic arm of autonomic nervous system. Acetyl cholinersterase is complex molecule containing two main subsites, the esteratic and the anionic sites. Positively charged nitrogen atom of Acetyl choline enzyme and negatively charged anionic site of acetyl cholinesterase form the Enzyme-substrate(EA) complex. The EA complex then undergoes acetylation and de-acetylaion at the serine hydroxyl group in the esteratic site which leads to the hydrolysis of the acetylcholine enzyme. The choline group which is formed is returned to the presynaptic neuron where acetyl choline is resynthesized form further action. One other type of acetyl cholinesterase is the plasma pseudocholinestrase which has high specificity for butrylcholine. The exact function of plasma pseudocholinestrase is still unknown but it is widely used for identifying acute organophosphorus poisoning.

We have so far discussed the mechanism of action of acetyl cholinesterase. In the next section we will discuss how organophosphorus compounds act to cause the cholinergic and nicotinic side effects.

The inhibition of Acetylcholinesterase takes place through a similar chemical reaction. The serine hydroxyl subsite combines with organophosphorous compound through acetylation. Unlike the easily reversible acetylation of the acetylcholinesterase enzyme , the phosphorylated compound maybe highly stable and sometimes be irreversible.

Mechanism of Activation

Most of the organophosphorous compound contain the P==S moiety which is metabolically inactive. During activation, the P==S moiety is converted to P==O moiety, which are a more reactive and less stable group when compared to the former group. The chemical conversion is mediated by a unique enzyme the Mixed function oxidase (MFO). Classical example of this chemical reaction is conversion of Parathion(inactive) to Paroxoan (chemically active and a strong anticholinesterase).(5)

Mechanism of Degradation

Organophosphorus compounds undergo hydrolytic (chemical or enzymatic hydrolysis) degradation to form metabolically inactive compounds. Enzymes which mediate the hydrolysis are called hydrolases or phosphotriester hydroloases.

After degradation, elimination of the Organophosphorus compound is mainly through urine and faeces.

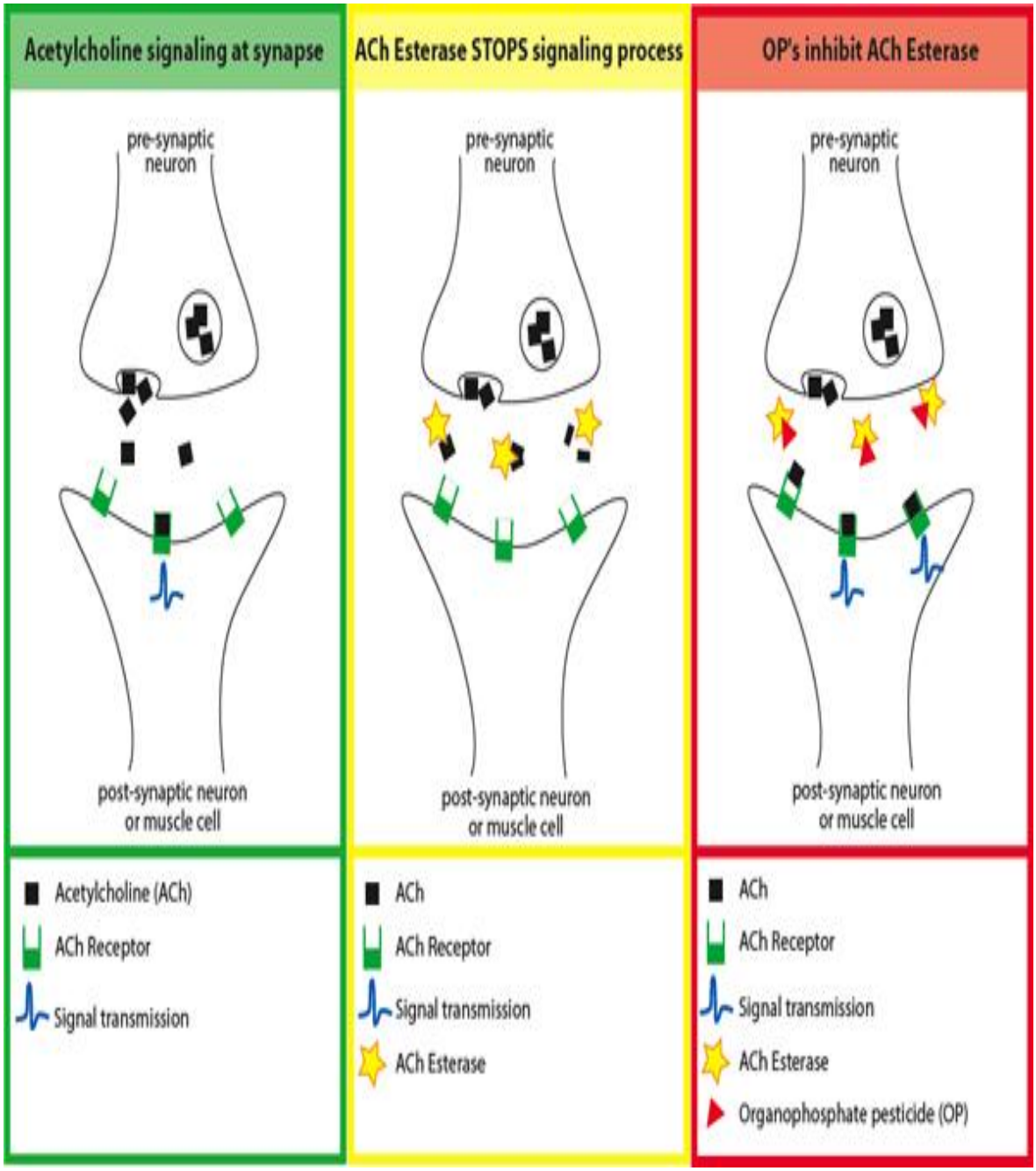


Figure 1 Mechanism of action of Organophosphorus compound

(Picture taken from organophosphates pesticides and child health(6).

CLASSIFICATION BASED ON LETHALITY

GHS (Global harmonised system) classification and WHO recommended classification are the most commonly used classification of organophosphorus compound based on their lethality.

Although the GHS classification is a widely accepted classification system, we have adapted the WHO recommended classification (2009 update) in this study.

The classification is done based the lethal dose (LD50) measures on rats both for oral as well as dermal exposure. Lethal dose (LD50) is amount of toxin (mg per kg of body weight) required for killing 50% of the population.

WHO Class		LD_{50} for the rat (mg/kg body weight)	
		Oral	Dermal
Ia	Extremely hazardous	< 5	< 50
Ib	Highly hazardous	5–50	50–200
II	Moderately hazardous	50–2000	200–2000
III	Slightly hazardous	Over 2000	Over 2000
U	Unlikely to present acute hazard	5000 or higher	

Table 1 WHO classification of Pesticides(2009 update)

(Table adapted from WHO recommended classification of pesticides by hazard and guidelines to classification)(7).

Some of the commonly used pesticides and their WHO class are as follows.

Class Ia – Methyl Parathion

Phorate

Class Ib - Triazophos

Dichlorvas

Monocrotophos

Class II - Chlorpyriphos

Phenthoate

Quinalphos

Dimethoate

Profenophos

Class III – Acephate

Malathion

CLASSIFICATION BASED ON TYPE OF COMPOUND

Organophosphorus compounds contain an alkyl group which can be either an methyl/ethyl/s-alkyl group. There are studies which have shown that poisoning with dimethyl compounds have a worse outcome when compared to poisoning with ethyl compounds.(8)(9) This may be attributed to the fact that dimethyl compounds have a shorter half life (half life of dimethyl – 3 hours, diethyl – 30hours) and a lower capacity for regeneration with oximes.(10).

Table 2 Classification of OP based on alkyl group

Dimethyl	Diethyl	S-alkyl
Monocrotophos	Phorate	Profenofos
Methylparathion	Triazophos	
Dichlorvas	Parathion	
Dimethoate	Quinalphos	
Phenthoate	Chlorpyriphos	
Malathion	Ethion	
Acephate		

CLINICAL MANIFESTATIONS

Clinical manifestations of organophosphorus poisoning can be divided as

1) Cholinergic manifestations
2) Neurological manifestations

CHOLINERGIC MANIFESTATIONS

Cholinergic manifestations can be further divided based on the type of receptors involved.(11)

1) Muscarinic symptoms – involving the muscarinic receptors
2) Nicotinic symptoms – involving the nicotinic receptors
3) Central symptoms – involving receptors in the central nervous system.

Cholinergic symptoms are described in the following table.

Table 3 Cholinergic manifestations of acute Op poisoning

MUSCARINIC	NICOTINIC	CENTRAL
Respiratory Bronchorrhea/bronchospasm Rhinorrhea		Anxiety Restlessness Convulsion
Cardiovascular Bradycardia Hypotension	Cardiovascular Tachycardia Hypertension	Insomnia Dysarthria Tremors
Gastro-intestinal Increased salivation Nausea/vomiting Abdominal pain Diarrhoea Fecal incontinence	Musculoskeletal Weakness Fasciculation Cramps Paralysis	Coma Absent reflex Cardiovasucular collapse Respiratory suppression
Genito-urinary Urinary incontinence		
Ocular Lacrimation Blurred vision(miosis)		

NEUROLOGICAL SYMPTOMS

Neurological manifestations of organophosphate poisoning have been described as early as in 1974 by Wadia et.al.(12)

Neurological paralysis as described by Wadia et.al was divided into the following categories.

1) Type 1a paralysis – present at admission and seen in patient who present early after the organophosphorus consumption(less than 4 hours).
   Wadia et al described 11 patients with Type 1a paralysis.

Type 1b paralysis – Present at admission and seen in patients who present late after organophosphorus consumption(later than 4 hours).

Type 1b paralysis was described in 10 patients in the same study.

Type 1 paralysis chiefly included bilateral pyramidal tract signs which respond well to treatment with atropine.

2) Type 2 paralysis – Paralysis which is not present at admission but which develops while on treatment with atropine.

Wadia et al had described type 2 paralysis in 36 patients in their study out of whom 15 patients had expired after requiring mechanical ventilation for different periods of time. They had also noticed that type 2 paralysis was not influenced by treatment with atropine and hence had concluded that type 2 paralysis was caused by nicotinic effects rather than muscarinic effects.

Other neurological manifestations described in this study were muscarinic effects such as miosis which almost universally present, impairment of consciousness was present in 10% of the patients, fasciculations were present in 27% of the patients, seizures were present in 1 % and toxic delirium(probably secondary to atropine treatment) was present in 50% of the patients.

Senanyake et al described and coined the ‘intermediate syndrome’ while describing paralysis in 10 patients with organophosphorus poisoning.(13)

Later studies done in our institution has shown that Type I and Type II paralysis may not be as distinct as described by Wadia et.al and the Type I and Type II paralysis maybe a continuum disorder that we refer to as the Type I-Type II continuum.(14)

DELAYED ORAGANOPHOSPHOROUS INDUCED PERIPEHRAL NEUROPATHY

Neurological manifestation of organophosphorous poisoning can be divided based on timeline of the symptoms.

Neurological manifestations which arise 1 – 4 weeks after acute organophosphorous poisoning has been described which are commonly referred to as Organophosphorous induced peripheral neuropathy (OPIDN).(15)

The manifestations are markedly different from the early neurological manifestations. These patients typically have peripheral nerve involvement and present with predominant motor neuropathy. They present with distal neuromuscular weakness involving lower limbs. Severe cases can have upper limb involvement also along with bilateral foot drop and wrist drop with depressed reflexes. Generally recovery is complete especially in the young and may take upto 3-6 months. Electrophysiological studies show decreased compound muscle action potential, increased distal latencies and nerve muscle biopsy have shown axonal degeneration and secondary demyelination.

Pathophysiology is still not fully understood although, Neuropathy target esterase (NTE) have implicated in the initiation of OPIDN.

DELAYED ORGANOPHOSPHOROUS ENCEPHALOPATHY (DOPE)

Encephalopathy has been described in patients with organophosphorus poisoning. Encephalopathy can manifest early in the course of the disease or can be a delayed manifestation. Delayed encephalopathy was described by Peter et.al in his study of 35 patients with acute organophosphate poisoning.(16) 3 patients had developed deep coma (GCS-2T) lasting for 4.3+/-2.1 days and 3 patients had developed low sensorium (GCS 3T-7T) lasting for 4.7+/-2.1 days. All 6 patients after variable duration of low sensorium (8+/-2 days) improved to normal sensorium and were discharged and alive.

The study had also noticed that all the 6 patients who had encephalopathy had intermediate syndrome.

The definition of delayed encephalopathy in this study was development of low sensorium after initial 72 hours of normal sensorium. The study had excluded patients who present with altered sensorium. But early encephalopathy has been described by Wadia et al in his study where 50% of the patients were reported to have toxic delirium. Hence it is clear that encephalopathic manifestations can an early or a delayed manifestation.

Early encephalopathy is predominantly attributed to central manifestations of the cholinergic crisis itself and respond to treatment with atropine. The pathophysiology behind delayed manifestations of encephalopathy is not fully understood. Probable mechanisms of delayed encephalopathy have been postulated. Administration of organophosphate induces excitatory changes in animal models which are suppressed by centrally acting anti-cholinergics such as atropine and CNS depressants such as diazepam.(17) Presence of persistently low

pseudocholinestrase at the onset of delayed encephalopathy suggests that acetylcholinesterase inhibition in the CNS may underlie the encephalopathy. Presence of intermediate syndrome in all patients who exhibited encephalopathy suggests a common mechanism which maybe involved in both the diseases.

But nevertheless, the study demonstrated bihemispheric slow wave disturbances in these patients suggestive of CNS depression rather than overstimulation as cause of the encephalopathy.

In our study, we have looked at the temporal profile of development of neuroparalysis and encephalopathy and the possibility that the central and peripheral manifestations of organophosphate poisoning as a continuum disorder rather than two separate disease processes.

ELECTROPHYSIOLOGICAL STUDIES

Electrophysiological abnormalities have been described in acute organophosphorus poisoning in 1987 by Wadia et.al. In this study, they had examined 66 patients who had presented with acute organophosphorous poisoning with and without weakness. Wadia et. al. had shown that the nerve conduction study was normal or mildly slowed, the compound muscle action potential showed reduction, repetitive nerve conduction studies showed possibility of neuromuscular junction abnormality and single muscle stimulation showed repetitive response.(18)

Serial neuro-electrophysilogical studies were done by Avasthi and was correlated with clinical weakness, serum cholinesterase and atropine dose in 19 patients with intermediate syndrome. He had shown that 30 Hertz repetitive nerve stimulation correlated well with weakness seen clinically (sensitivity = 61.72%; specificity = 81.54%; PPV= 73.91%; NPV = 71.62%) and concluded that it could be a useful marker for identifying intermediate syndrome.(19)

The largest electrophysiological study was done by Jayawardene et al where they had performed repetitive nerve stimulation in the right and left median and ulnar nerve at low and high frequencies.

Important finding from this study were:-

a) They had shown patients preceding the weakness had a decrement-increment pattern.
b) Initially when developing weakness the patients showed decrement-increment pattern only in high and intermediate frequencies and as the

weakness progressed the decrement-increment pattern was seen in low frequencies as well.

c) Severe decrement pattern and subsequent CMAPS not returning to the first CMAPs also was noted in patients with severe weakness and respiratory failure.

In the same study, Jayawardene had noted that electrophysiological changes were present in patients who did not have clinical weakness and preceding the development of intermediate syndrome. These observations lead her to propose the idea that the Type I and Type II weakness were not separate disease entity and they were probably a spectrum disorder. Patients with electrophysiological changes and with either no clinical weakness or mild to moderate weakness were termed 'forme fruste' intermediate syndrome.

A proposed electrophysiological criteria for diagnoses of intermediate syndrome was hence proposed and is presented in the following table.

Table 4 Proposed Electrophysiological Criteria for IMS spectrum diagnosis.

IMS spectrum	**Clinical weakness**	**Electrophysiological changes**
None	None	None
Forme fruste IMS, Stage I	None	D-I at high frequencies
Forme fruste IMS, Stage II	Mild	D-I at intermediate and high frequencies
Forme fruste IMS, Stage III	Moderate to severe	D-I at all frequencies
Forme fruste IMS, Stage IV	Moderate to severe	D-I and repetitive fade
IMS	Moderate to severe	Severe decrement
IMS with respiratory failure	Severe with respiratory failure	Severe decrement followed by progressive decrements.

Materials

and

Methods

Materials and Methods

Type of study

This is an observational study conducted between November 2013 to August 2014.

Study approval

The study was approved by the Institutional Review Board in April 2013.

Sample Size

The sample size calculation is based on previous studies done on Intermediate

Syndrome and organophosphorus poisoning. The incidence of Intermediate syndrome in

Organophosphorus poisoning is 37 % based on the study done by Dr. Lovely et.al in our institution in 2010. With an anticipated odd's ratio of 4 and the study is powered to detect 80% difference and 5 % level of significance the sample was calculated to be 169.

Proportion of the disease : 0.375

Anticipated odd's ratio : 4

Power of the study(1-beta)% : 80

Alpha Error : 5

Multiple correlation coefficient : 0.41

Sample size : 169

Since the study involves detailed clinical examination with daily neurological examinations and electrophysiological studies , it was decided to keep a feasible sample size of 80 in this study.

METHODS

Patient selection

The study participants were enrolled from the accident and emergency department,Christian Medical college who satisfied the following inclusion criteria.

Inclusion criteria:

1) Age above 15 years.

2) Patients with history of consumption of organophosphorous pesticide poisoning.

3) Patients presenting within 72 hours after consumption of organophosphorous compound.

Case Ascertainment:

1) Patients who present with alleged history of organophosphorous poisoning with an identified compound.

2) Patients who present with alleged history of organophosphorous poisoning with typical toxidrome, and low butylcholinesterase levels.

3) Patients who present without an alleged history of poisoning but with typical toxidrome of OP poisoning and low butylcholinesterase levels.

Exclusion criteria:

All children below the age of 15 years and pregnant women.

Patients who have been managed in other hospitals for more than 72 hours have been have been excluded.

Informed consent was taken for all participants after they satisfy the inclusion and exclusion criteria before enrolling them in the study. The recommended treatment guidelines for management of organophosphorus poisoning were followed.

The baseline characters,demographic details, organophosphorus compound details ,details of date and time of consumption, details regarding treatment undergone in other hospitals and clinical profile of participant at admission in accident and emergency were recorded in the patient proforma.

If the patient presented within 24 hours of consumption of the organophosphorus compound electromyography and nerve conduction studies were done after admission in the medical wards ,high dependency unit or intensive care unit.

After admission, the participants were followed daily and clinical examination to look for features of encephalopathy and intermediate syndrome were recorded in the patient proforma.

INTERMEDIATE SYNDROME DEFINITION

Intermediate syndrome is defined as development of proximal muscle weakness of MRC grading 3 or less along with extra-ocular, neck and respiratory muscles weakness developing after 72 hours of consumption of the organophosphorus compound, which may or may not require mechanical ventilation.

Senenyake et.al were the first to describe intermediate syndrome in patients with acute organophosphorus consumption and they had defined intermediate syndrome as development of proximal muscle weakness developing 24-96 hours after the consumption of organophosphorus compound and after the acute cholinergic crisis has settled.

Although Wadia had described this type of weakness in his studies as type 2 paralysis Senanyake had coined the term Intermediate syndrome.

The defiintion of Intermediate syndrome used in this study has been adapted from the definition proposed by John and Khan,from studies which were published in our institution.

Based on the timing of development of weakness we have divided the patients into following categories.

Category 1 – Type 1 weakness alone

Category 2 – Type 1 weakness followed by Type 2 weakness(Type 1-2 continuum)

Category 3 – Type 2 weakness alone.

Category 4 – No muscle weakness.

Namba scale

Namba scale has been used widely for assessment of severity of poisoning in patients who present with acute organophosphorus poisoning

Table 5 Namba Scale

Namba grade	Clinical presentation
Namba 1 or Latent	No clinical manifestations Severity assessed by measurement of serum cholinesterase levels which is inhibited by 10-50 % of normal.
Namba II or mild	The patient can walk but complains of dizziness, headache, numbness of extremities, nausea and vomiting, excessive sweating and salivation, tightness in chest ,abdominal cramps or diarrhoea. Serum cholinesterase level is 20-50% of normal.
Namba III or Moderate	The patient cannot walk and there is generalised weakness, difficulty talking, muscular fasciculation, miosis. Cholinesterase level is 10-20% of normal
Namba IV or Severe	Unconsciousness, marked miosis and loss of pupil reflex to light, muscular fasciculation, flaccid paralysis, secretions from the mouth and nose ,moist rales in the lungs ,respiratory difficulty and cyanosis. Serum Cholinesterase levels are less than 10% of normal.

(Table adapted from Americal Journal of medicine, Poisoning due to organophosphate insecticides.Acute and chronic manifestations, 50 (4); 475-492; 1971)

Predictive scoring system

Currently there are no treatment options available for intermediate syndrome except for supportive management in the form of mechanical ventilation and careful observation of the patient with acute organophosphorus poisoning.

In our institution, all organophosphorus poisoning patient are observed for minimum of 5 days after consumption. Based on the patients clinical condition they are either admitted in Medical high dependency unit or Semi-intensive care beds in the ward.

In this study we have proposed to develop a predictive scoring system which would be able to predict the development of intermediate syndrome in patients with OP poisoning at admission. If we are able predict the development of intermediate syndrome on first day, the patients can be managed accordingly and their level of care can be ascertained at admission itself.

We have formulated the predictive scoring system from a study done in our institution by Lovely et.al.

The study was done to assess the risk factors for developing intermediate syndrome and the risk factors identified in the study were

1) Neck muscle weakness at admission
2) Namba scale at admission
3) Glasgow-coma scale at admission
4) WHO Class of organophosphorus compound
5) Type of organophosphorus compound

The study had demonstrated that neck muscle weakness and Namba severity at admission were statistically significant risk factors for development of intermediate syndrome.

The other risk factors were included in the formulation of the predictive scoring system even though they did not achieve statistical significance as the study did not have sufficient sample size to ascertain the statistical significance.

Formulation of Predictive scoring system:

In order to assess the significance of risk factors, the data from the study were re-analysed. Logistic regression and multivariate analysis was done on the preliminary data from the study done Lovely et.al. The results of the same have been shown below. The risk factors were analysed based on multiple logistic regression and their significance calculated. The maximum score was given to neck muscle weakness as this single risk factor that was significantly associated with development of IMS (p value – 0.05).

Table 6 Multivariate analysis of risk factors

	Odd's ratio	Confidence interval		P value
		Lower limit	Upper Limit	
WHO class	1.399	0.14	13.66	0.77
Type of Compound	1.32	0.14	11.99	0.81
Neck muscle weakness	**8.29**	**0.99**	**69.45**	**0.05**
GCS	1.79	0.36	5.34	0.60
Namba	4.35	0.37	51.33	0.24

Table 7 Predictive scoring system

Risk factors	Maximum score	Minimum score
Muscle weakness at admission	4	0
Severity assessed by Namba	3 / 2	1
Glasgow coma scale at admission	2	1
WHO class of compound	2	1
Type of compound	2	1

Components of the scoring system:

1) Muscle weakness at admission:

   Muscle weakness will be assessed clinically at admission. Muscle weakness will be defined as MRC grading of less than or equal to 3 in the proximal muscles or a poor effort to lift the neck entirely off the bed. If muscle weakness is present it will be given 4 points, and if absent it will be given 0 points.

2) Severity assessed by Namba scale:

   Severity of poisoning will be assessed by Namba scale as described earlier.

   Latent → 0 point

   Mild → 1 point

   Moderate → 2 points

   Severe → 3 points

3) Mental status assessed by Glasgow coma scale:

   Altered mental status (GCS <13/15 or < 8t/15) will be given 2 points and any GCS better than previously mentioned will be given 1 point.

4) WHO class of compound:

   WHO class I and II : 2 points

   WHO class III : 1 point

5) Type of compound :

Di-methyl compound : 2 points

Others : 1 point

Maximum score at admission: 13

Minimum score at admission: 3.

The predictive score was calculated at the time of admission of the patient to the hospital. This would help in preventing potential bias of the investigator towards awarding higher scores to patients.

The usefulness of the predictive scoring would be calculated using receiver operator curves and the sensitivity and specificity will be calculated.

Statistical

Analysis

Statistical analysis

Data entry was done using Epidata version 3.1.Data analysis was done using SPSS version 16.0.Univariate and multivariate analysis was done on the data to identify risk factors and their significance in development of intermediate syndrome. Logistic regression was done.

Receiver operating curve was done to assess the predictive scoring system and it association with the development of intermediate syndrome.

Results

BASELINE CHARACTERISTICS

The study was conducted between November 2013 and August 2014. Between this time 78 patients were recruited into the study. The mean age of the participants of the study was 31.27, with slight male (63%) preponderance. We were able to identify the organophosphorous compound in 69 out of 78 patients. The mean pseudocholinesterase levels were 1845 (Lowest – 37 and Highest – 10,725) and 34 (43.5%) patients had presented with severe poisoning as assessed by Namba severity score. Three-fourth of the patients had received treatment in a local hospital before presenting to us. The most common treatments given were gastric lavage, pralidoxime and atropine.

Table 8 Baseline Characteristics

PROFILE		VALUE
Total participants		78
Age mean(SD)		31.27(11.97)
Male : female ratio(percentage)		49(63%):29(37%)
Compound identified (%)		69 (88.5%): 9 (11.5%)
Pseudocholinestrase levels - mean		1845
Prior treatment (%)		57 (73%) : 21 (27%)
With Gastric Lavage		44(56%)
With Oximes		13(17%)
With Atropine		28(37%)
Severity of Poisoning Namba scale (%)	Latent	5(6.5%)
	Mild	17(22%)
	Moderate	22(28%)
	Severe	34(43.5%)
WHO class (%)		
I		28(40.5%)
II		31(45%)
III		10(14.5%)
Type (%)		
Dimethyl		22(32%)
Diethyl		36(52%)
Others		11(16%)

TYPE OF PARALYSIS

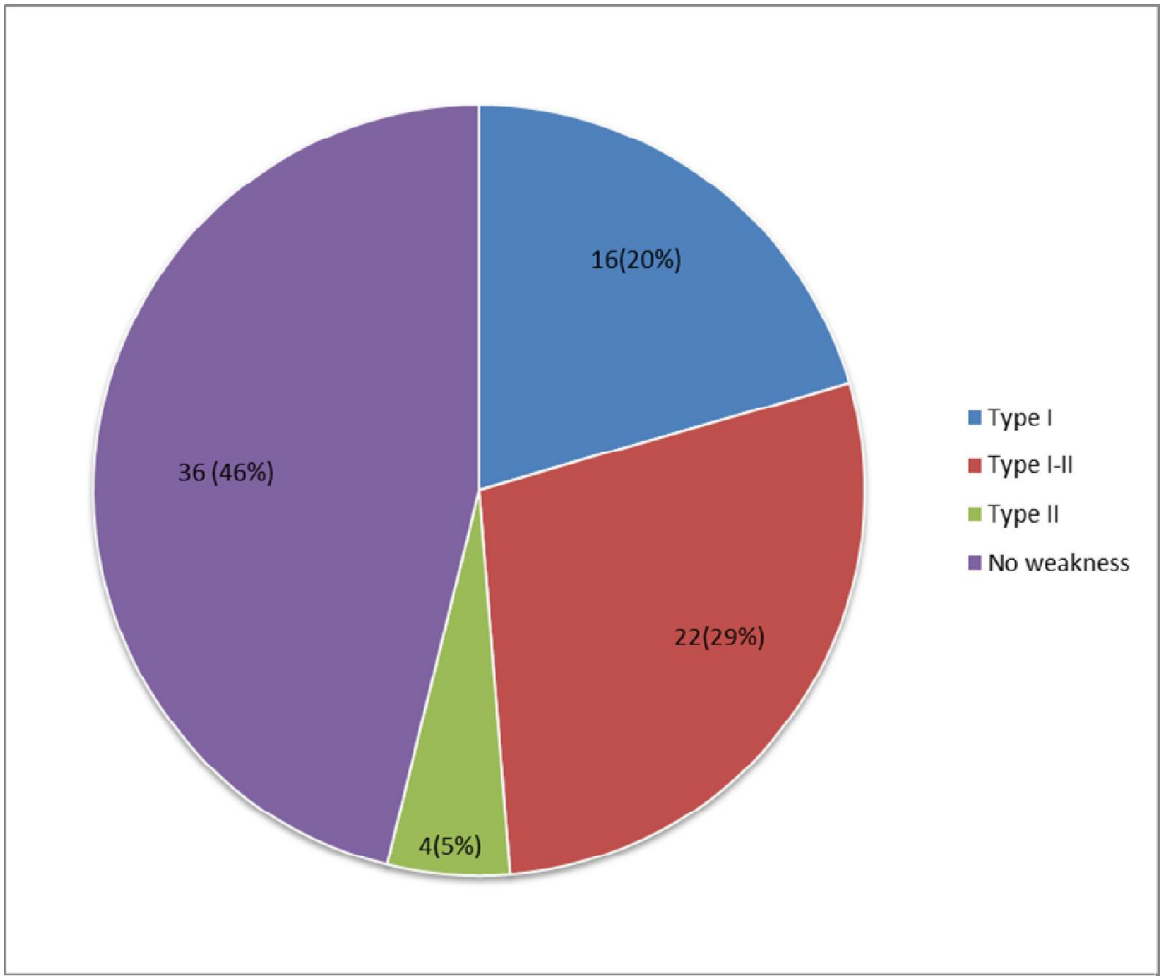


Figure 2 Type of paralysis seen among the study patients

36(46.2%) patients did not develop any weakness during hospital admission. 16 (20.5%) patients developed only Type I paralysis which recovered. 26 (33.3 %) patients developed Type II paralysis. Of these patients 22(28.2%) presenting with Type I paralysis persisted to have paralysis for more than 72 hours(Type I-II paralysis continuum). Only 4(5%) patients had developed new onset weakness after 72 hours without prior development of prior Type I paralysis (pure Type II paralysis).

ORGANOPHOSPHORUS COMPOUND PROFILE

TYPE OF COMPOUND

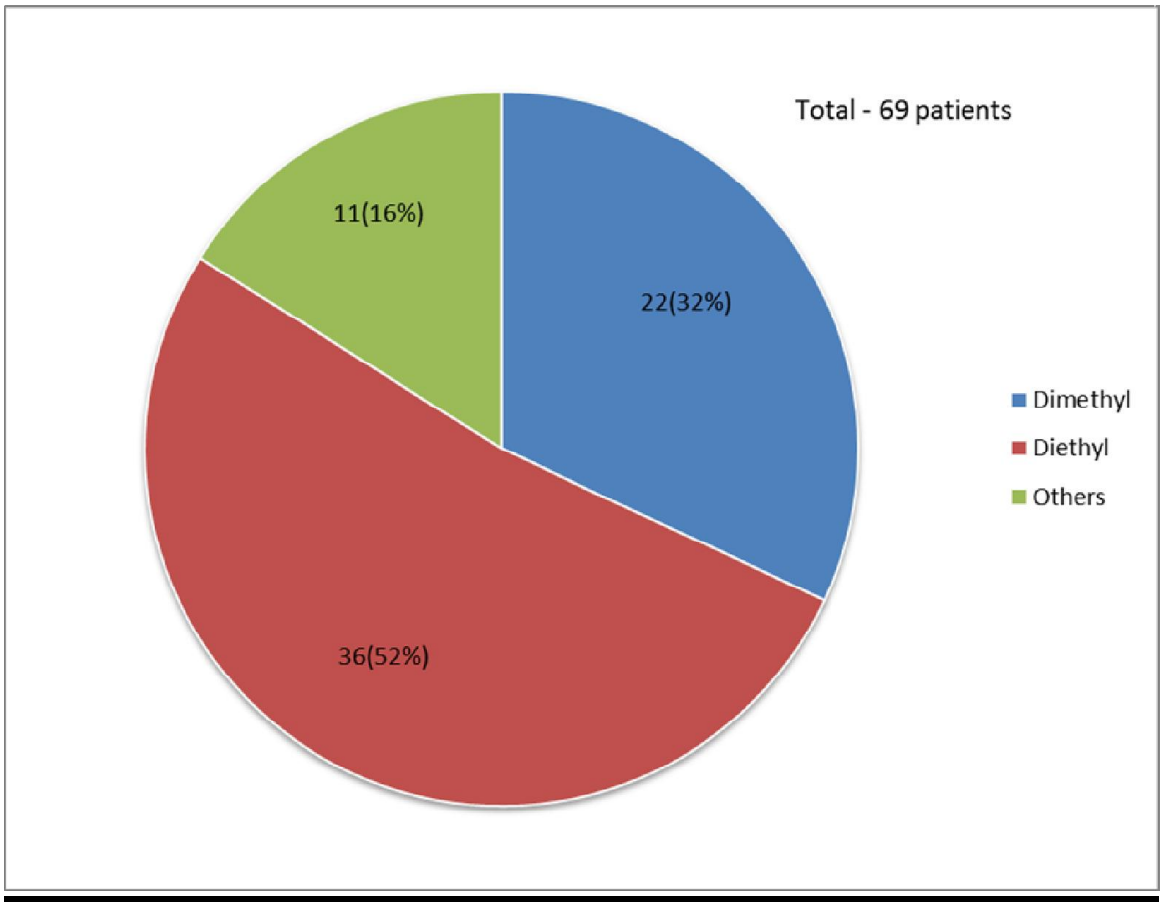


Figure 3 Different types of compounds ingested

22(32%) patients had ingested an organophosphorus compound belonging to the dimethyl group while 36(52%) patients had ingested a diethyl compound. 11(16%) patients had ingested compound belonging to s-alkyl group and others.

Rest of the 9 patients the compound was not identified.

WHO CLASS OF COMPOUND

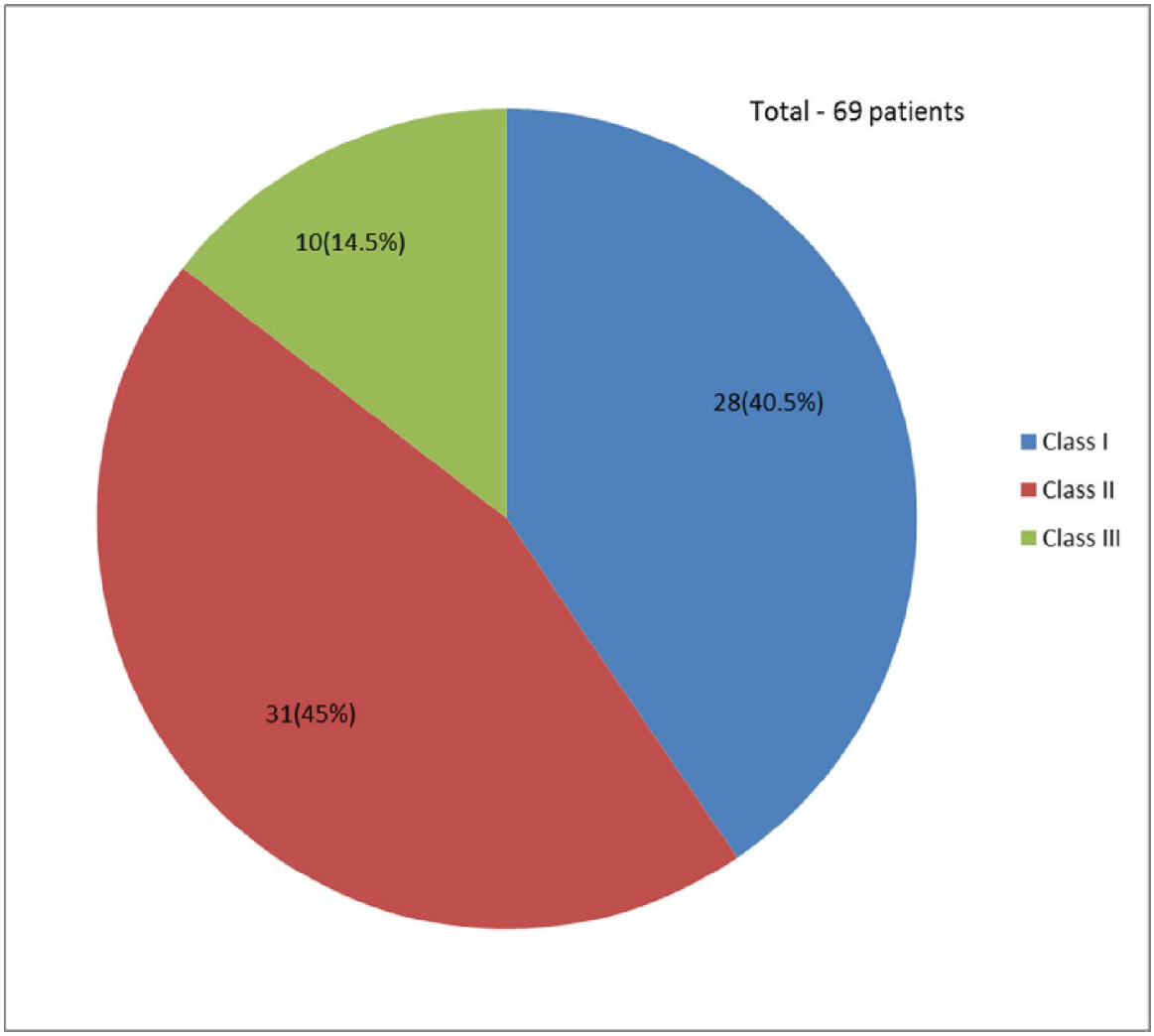


Figure 4 WHO class of compound

85 % of the patients had ingested compounds which belonged to WHO class I(n=28) and WHO Class II(n=31) while 15% of the patients had ingested compounds which belonged to WHO class III(n=10). Rest of the 9 patients the compound was not identified.

FREQUENCY OF INDIVIDUAL COMPOUNDS

Table 9 Frequency of Individual compounds

Compound	Number	WHO class	Type
Quinalphos	11	II	Di-ethyl
Monocrotophos	10	I	Di-methyl
Profenophos	10	III	S-alkyl
Chlorpyriphos	9	II	Di-ethyl
Phorate	9	I	Di-ethyl
Dimethoate	8	II	Di-methyl
Triazophos	4	I	Di-ethyl
Methylparathion	4	I	Di-methyl
Phenthoate	2	II	Di-methyl
Dichlorvas	1	I	Di-methyl

69 out of 78 patients enrolled in the study had the organophosphorous compound identified. The compound was identified if the patient/relative had recalled the name by themselves or some patients had either brought the leaflet of the pesticide consumed or the bottle containing pesticide along when they presented to accident and emergency department. The method of

compound identification was as follows: Name given by the patient/relative – 19.4%(n=13); Leaflet brought – 35.8% n=24) and Bottle brought – 44.8%(n=30). The most frequently ingested compounds in order of frequency were: Quinalphos, Monocrotophos, Profenophos, Chlorpyriphos, Phorate and Dimethoate. These 5 compounds together contributed to 82.6% of compounds ingested.

TREATMENT RECEIVED IN OTHER HOSPITALS

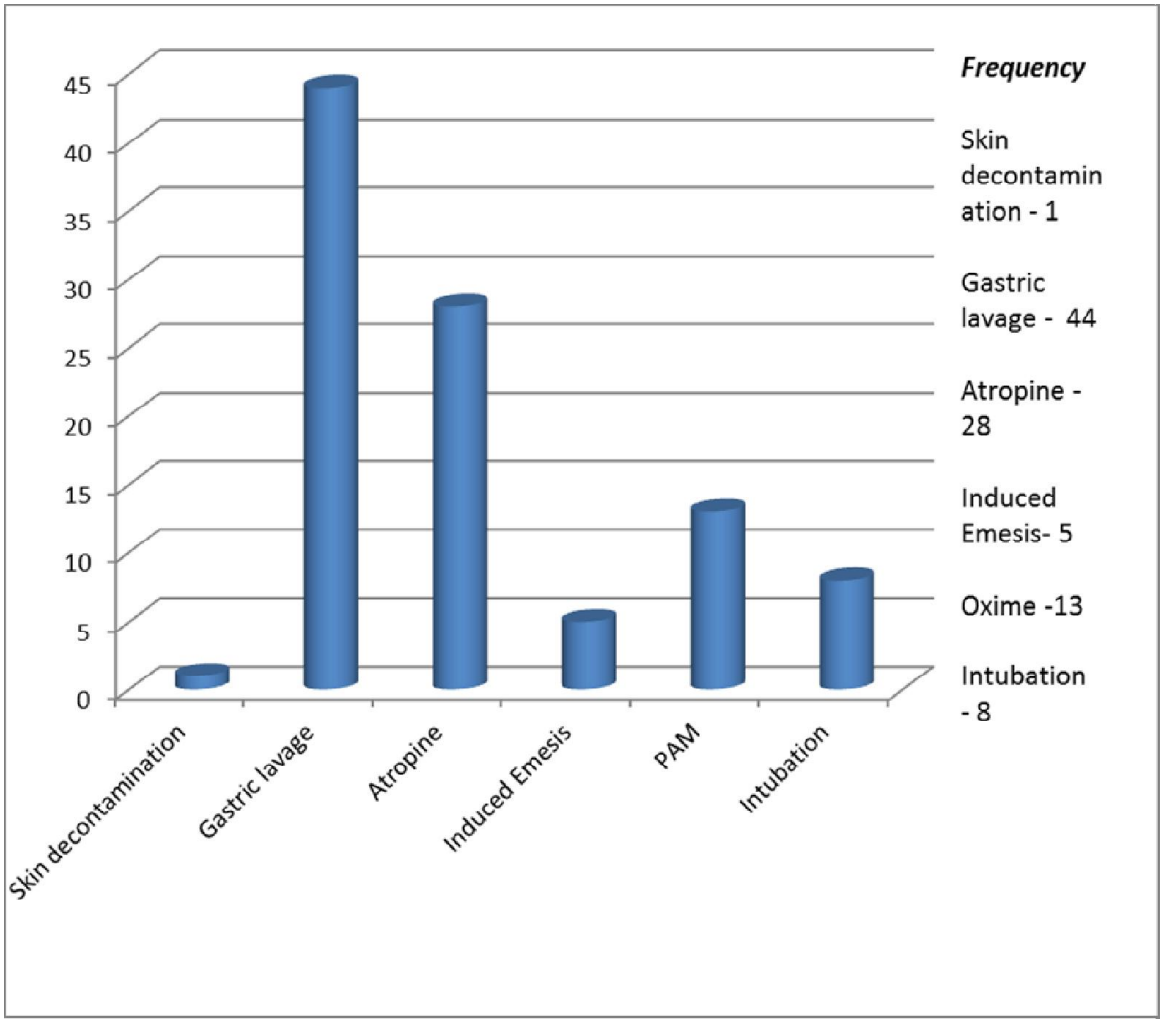


Figure 5 The details of treatment received in other hospitals

57(73.1%) patients had presented to a local hospital before being referred to our centre. The most common treatment offered were gastric lavage (77.2%), pralidoxime (23%) and atropine(49%). The mean duration for patients to reach a hospital for first medical treatment was 90 minutes (minimum duration – 10 minutes and maximum duration – 6 hours). The mean duration patients took to reach our centre was 5.4 hours(minimum duration – 15 minutes and maximum duration -2 days).

As seen above, there is a considerable delay in patients reaching our centre for treatment. This is because our centre is a tertiary care hospital and hence patients are referred to our hospital after first line treatment in a local hospital.

CLINICAL OUTCOMES

TOXIDROME AT PRESENTATION

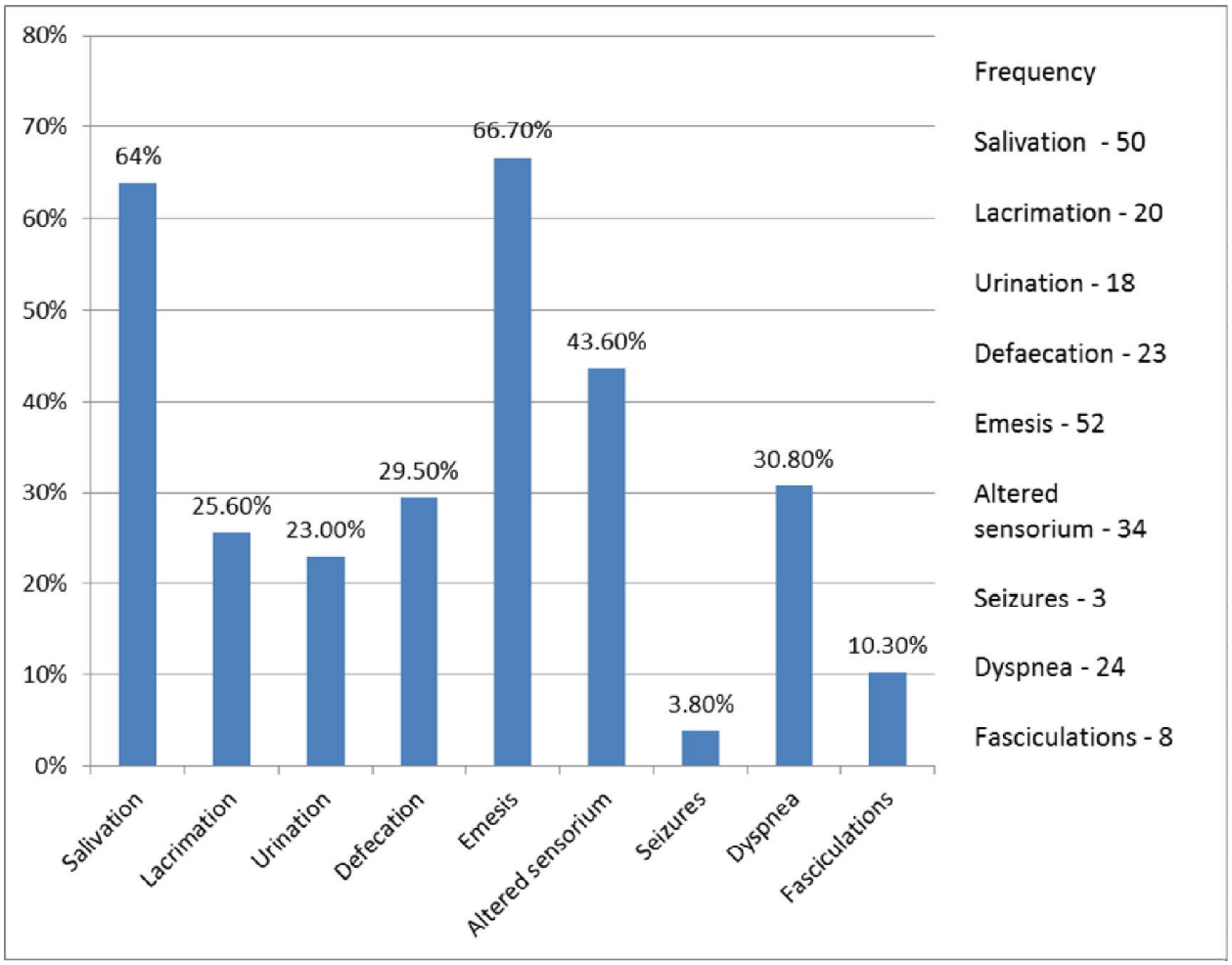


Figure 6 Signs and symptoms of toxidrome at presentation

Most common presenting symptoms and signs at admission were were salivation (64%), vomiting (66.7%) and altered sensorium (43.6%). – 73 out of

78 patients (94%) of patients had cholinergic signs are presentation. 8 patients had (10.3%) had fasciculations at presentation.

SEVERITY OF POISONING ASSESSED BY NAMBA SCALE

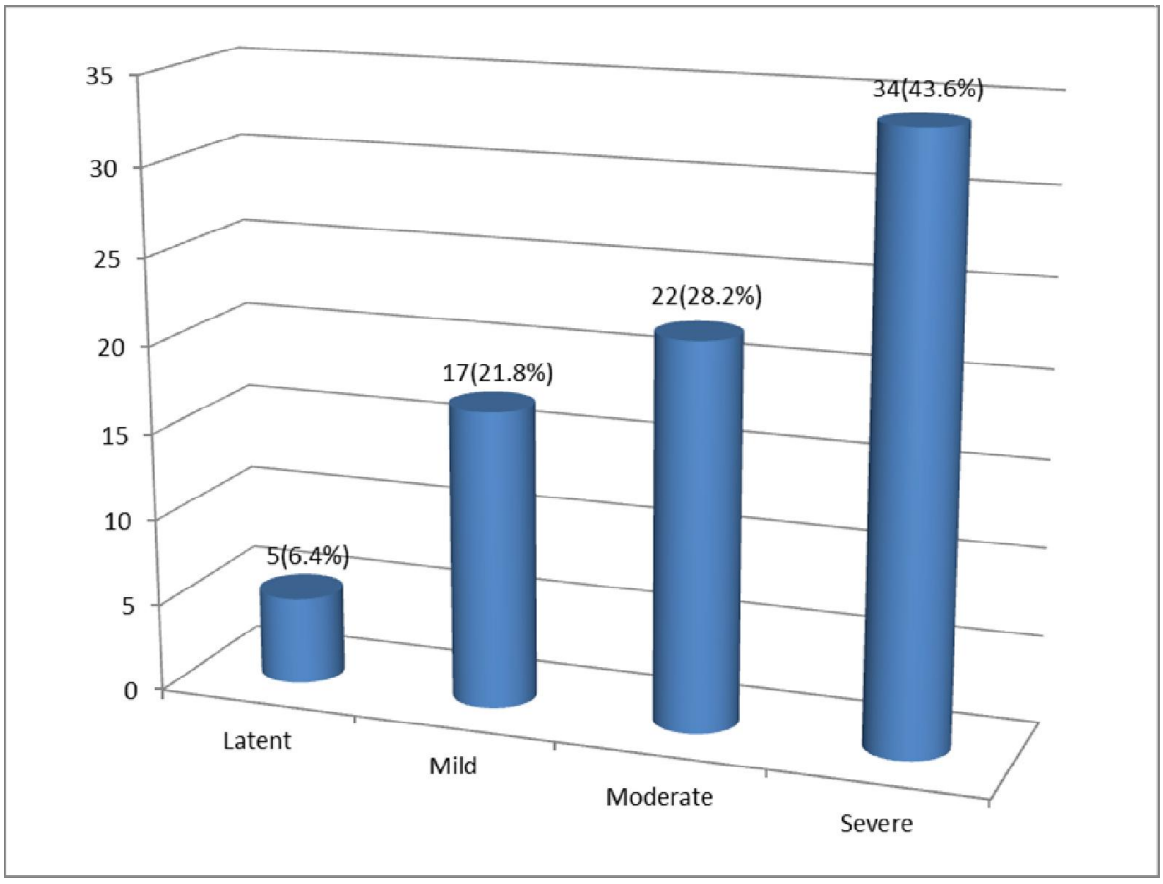


Figure 7 Severity assessed by Namba scale

Namba severity scale was used to assess the severity of cholinergic crisis at admission. 5 (6.8%) had no signs or symptoms (latent poisoning). 21.8 % had mild severity. The majority of patients (71.8%) had moderate to severe poisoning. This reflects the profile of patients at a referral centre.

SENSORIUM ASSESSED BY GLASGOW COMA SCALE

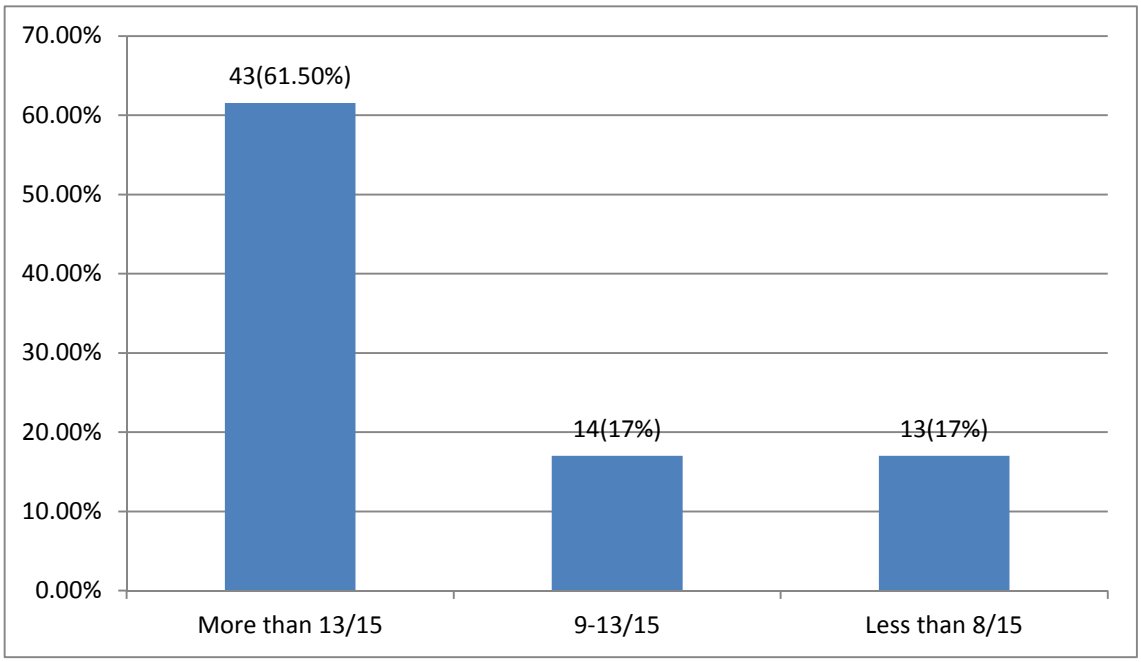


Figure 8 GCS at admission in non-intubated patients patients

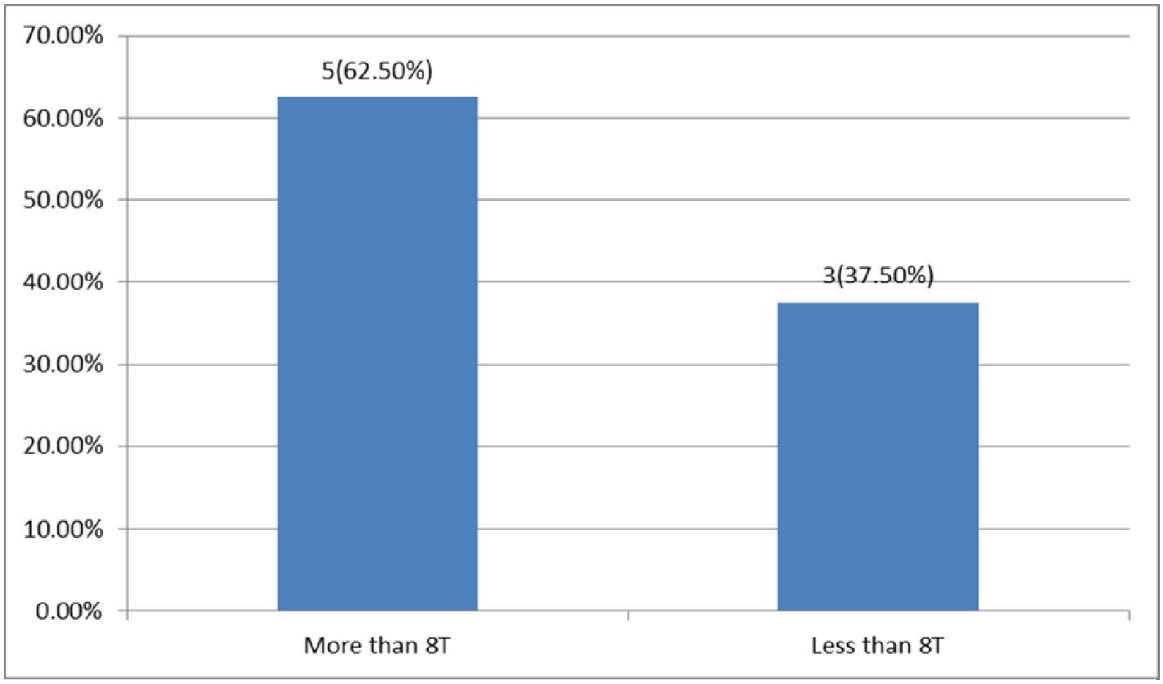


Figure 9 GCS at admission among already intubated patient

8 out of the 78 patients enrolled in the study were intubated outside. Above graphs depicts patients GCS at admission(Fig 8 – Patients who were intubated in local hospitals).Among patients who were intubated elsewhere 3 out of 8 patients had a GCS less than 8T/15 whereas 5 out of the 8 patients had normal sensorium.

Among the non-intubated patients, 61%(n=43) of the patients had presented with normal sensorium(GCS >13/15) and 34%(n=27) of the patients had sensorium lower than 13/15.

PATIENT PROFILE ACCORDING TO PUPIL SIZE AT ADMISSION

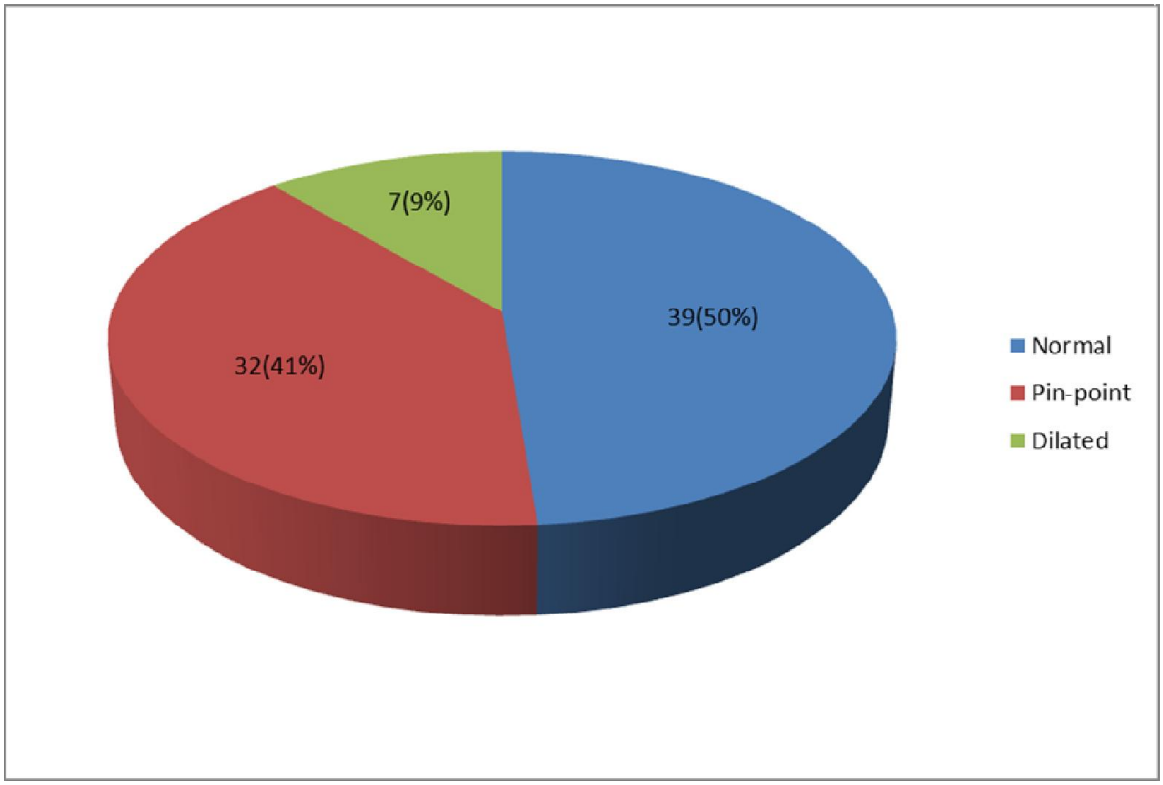


Figure 10 Patient profile according pupil size at admission

41% (n=32) of the patients had pupil size less than 2 mm at presentation (secondary to acute cholinergic crisis). 9%(n=7) of the patients presented with pupil size more than 5 mm(probably secondary to atropine received in the primary treatment centre).50% of the patients had normal pupil size at presentation.

NECK MUSCLE WEAKNESS AT ADMISSION

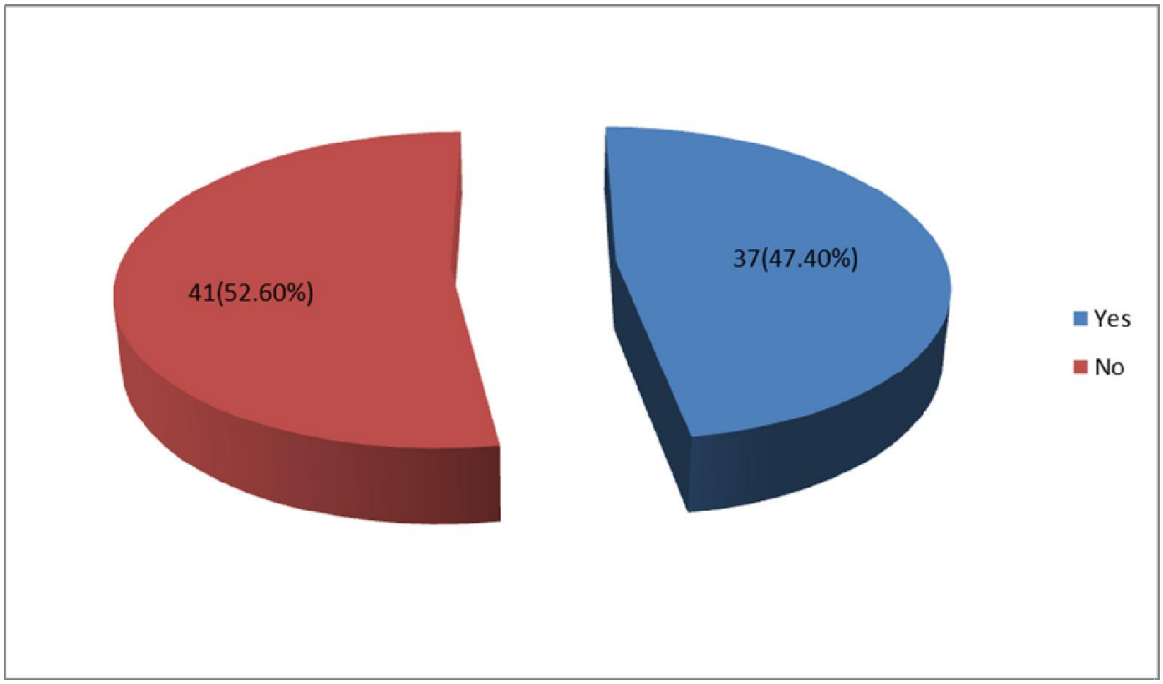


Figure 11 Patient profile according to neck muscle weakness at admission

37(47.4%) patients had neck muscle weakness at admission while 41 patients did not have any features of weakness.10(12.8%) patients had fasciculations present at admission. 9 out of the 10 patients who had fasciculation also had neck muscle weakness.

NEUROLOGICAL OUTCOME

NEUROMUSCULAR WEAKNESS

TYPES OF PARALYSIS

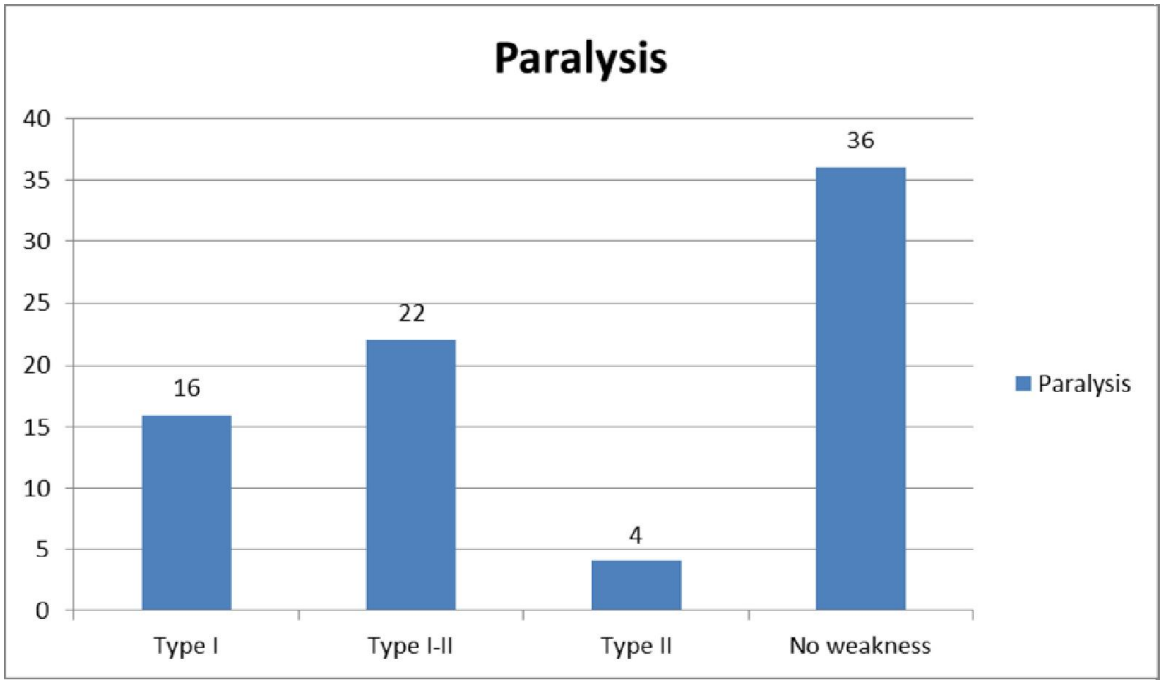


Figure 12 Distribution of patients according to types of paralysis

36(46.2%) patients did not develop any weakness during hospital admission. 16 (20.5%) patients developed only Type I paralysis which recovered. 26 (33.3 %) patients developed Type II paralysis. Of these patients 22(28.2%) presenting with Type I paralysis persisted to have paralysis for more than 72 hours (Type I-II paralysis continuum). Only 4 patients had

developed new onset weakness after 72 hours without prior development of prior Type I paralysis (pure Type II paralysis).

PATTERN OF TYPE I WEAKNESS

Type I weakness is defined as weakness which is present at admission and which resolves within 72 hours after consumption of the organophosphorus compound.

The table 10 below shows the pattern of Type 1 weakness, such as neck muscle weakness at admission, namba severity, duration of muscle weakness and duration of mechanical ventilation, lowest power recorded in the proximal muscles around the shoulder and hip, as assessed by MRC grade and deep tendon reflexes assessed in the knee.

Table 10 Description of individual patients with Type 1 weakness

Serial number	Neck muscle weakness at admission	Namba scale at admission	Duration of muscle weakness	Duration of Mechanical ventilation	Lowest Power Shoulder	Lowest Power Hip	Deep Tendon Reflex knee
1	Yes	Severe	1	3	4	4	2+
7	Yes	Severe	2	4	4	4	2+
16	Yes	Moderate	2	0	5	5	1+
17	Yes	Moderate	2	0	5	5	1+
20	Yes	Severe	1	2	4	4	2+
26	Yes	Severe	1	3	4	4	2+
42	Yes	Severe	1	5	4	4	2+
43	No	Severe	2	2	4	4	2+
50	Yes	Severe	1	3	5	5	2+
52	Yes	Mild	1	2	4	4	2+
55	Yes	Severe	2	6	3	3	2+
59	Yes	Severe	3	3	4	4	Ab
60	No	Severe	3	4	4	4	1+
66	Yes	Severe	2	0	4	4	2+
71	Yes	Moderate	1	0	4	4	1+
72	yes	Moderate	1	0	4	4	2+

16(20.5%) patients out 78 patients had type I weakness. 14(88%) patients had neck muscle weakness at admission. 15(94%) had moderate to severe poisoning on Namba scale assessed at admission. The mean lowest power in upper limb was 4.07 and in the lower limb was 4.06 . Mean duration of weakness was 1.63 days varying from 1-3 days. 11(68.8%) patients out of 16 patients with Type I weakness required mechanical ventilation. Mean duration of mechanical ventilation of 2.3 days. All patients except one had intact deep tendon reflexes and 4 had diminished reflexes.

PATTERN OF TYPE II WEAKNESS

Type I-II continuum weakness is when the patient develops muscle weakness within the first 72 hours of consumption and the muscle weakness persists for more than 72 hours.

The table 11 below shows the pattern of Type I-II contiuum weakness such as neck muscle weakness at admission, namba severity, duration of muscle weakness and duration of mechanical ventilation, lowest power recorded in the proximal muscles around the shoulder and hip as assessed by MRC grade and deep tendon reflexes assessed in the knee.

Table 11 Description of Type I-II continuum weakness

Serial Number	Neck muscle weakness at admission	Namba scale at admission	Duration of muscle weakness	Duration of Mechanical Ventilation	Lowest Power Shoulder	Lowest Power Hip	Deep Tendon Reflex Knee
77	Yes	Severe	38	37	2	2	Ab
61	Yes	Severe	11	11	3	3	Ab
22	Yes	Severe	6	8	4	4	2+
33	Yes	Moderate	5	4	4	4	1+
51	Yes	Severe	4	3	4	4	1+
78	Yes	Severe	10	10	3	3	2+
31	Yes	Moderate	8	9	4	4	1+
73	Yes	Severe	11	11	2	2	Ab
67	Yes	Severe	5	9	4	4	3+
12	Yes	Severe	9	14	3	4	Ab
32	Yes	Severe	2	3	4	4	2+
3	Yes	Severe	9	10	4	4	2+
74	Yes	Severe	13	15	2	2	2+
41	Yes	Severe	4	4	3	3	2+
73	Yes	Severe	12	11	2	3	1+
25	Yes	Severe	4	5	3	3	1+
75	Yes	Severe	20	22	2	3	Ab
79	Yes	Severe	4	2	3	2	1+
45	Yes	Moderate	4	5	3	3	Ab
8	Yes	Severe	10	14	3	3	2+
63	Yes	Severe	5	5	3	3	1+
40	Yes	Severe	15	18	3	4	1+

22(28.2%) patients out of 78 patients had developed Type I-II continuum weakness. All the patients had moderate to severe poisoning. All the patients had neck muscle weakness at admission which persisted beyond 72 hours after consumption of OP compound. The mean lowest power in the upper limb was 3.04 and the mean lowest power in the lower limb was 3.05 . Mean duration of muscle weakness was 9.2 days. All patients required mechanical ventilation and mean duration of ventilator days was 10.45 days. 6 patients had absent deep tendon reflexes and 8 had diminished reflexes.

PATTERN OF TYPE II WEAKNESS

Type II weakness is described as weakness which develops 72 hours after consumption of the organophosphorus compound.

Table 12 Description of individual patients with Type II weakness

Serial Number	Namba score	Neck muscle weakness at admission	GCS at admission	Duration of paralysis	Duration of Mechanical ventilation	Lowest Power Shoulder	Lowest Power Hip	Deep Tendon Reflex Knee
2	Moderate	No	15/15	5	0	4	5	2+
27	Mild	No	15/15	9	9	2	2	Ab
53	Moderate	No	11/15	9	14	3	3	2+
68	Moderate	No	15/15	5	5	3	3	1+

4(5.1%) patients out 78 patients had developed muscle weakness 24 to 72 hours after consumption of OP compound. 3 patients required mechanical ventilation and mean ventilator days was 9.33 days and mean duration of muscle weakness was 7.0 days. One patient expired during the study period belonged to this group (cause of death was ventilator associated pneumonia and septic shock).

Table 13 Comparison between clinical finding in Type I, I-II & II weakness

	TYPE I WEAKNESS	TYPE I-II WEAKNESS	TYPE II WEAKNESS
Number of patients	16	22	4
Neck muscle weakness at admission (%)	14(87.5%)	22 (100%)	Nil
Neck muscle weakness during course of illness (%)	16 (100%)	22(100%)	4(100%)
Namba scale Mild **Moderate** **Severe**	1(6.3%) 4(25%) 11(68.7%)	Nil 3(13.6%) 19(86.4%)	1(25%) 3(75%) Nil
Upper limb – proximal muscle weakness (%)	13(87%)	22(100%)	4(100%)
Mean lowest power in the upper limb (SD) **Range**	4.07(0.46) 3 – 5	3.04(0.89) 1 - 4	2.75(0.96) 2 - 4
Mean lowest power in the Lower limb (SD) **Range**	4.06(0.45) 3 – 5	3.05(0.99) 1 - 4	2.5(1.29) 1 - 4
Mean duration of weakness in day in days (SD) **Range**	1.625 days(0.71) 1 – 3 days	9.5 days(7.74) 4 -38 days	7 days(2.3) 5 – 9 days
Mechanical Ventilation (%)	11(68.8%)	22(100%)	3(75%)
Mean duration of mechanical ventilation in days (SD) **Range**	3.3 days(1.28) 3 – 6 days	10.45 days(7.89) 2 – 37 days	9.33 days(4.5) 5 – 14 days
Lower limb – proximal muscle weakness (n/%)	13 (81.3%)	22(100%)	4(100%)
Knee reflex – n (%) **Proportion with diminished reflexes** **Proportion with Absent reflexes**	 4 (25%) 1(6.25%)	 8(36.4%) 6(27.3%)	 1(25%) 1(25%)

From the above table 13, which summaries clinical findings in patients with different types of paralysis we can see that type I and I-II paralysis occurs more commonly than type II paralysis. Neck muscle weakness was present in all patients belonging to all categories. The patients belonging to different types of paralysis exhibited paralysis in similar groups of muscles (mainly neck muscle and proximal muscle weakness). Although the muscle groups affected were similar the degree of weakness was more severe in the Type II and Type I-II group when compared to the Type I group. Lowest power documented was lower in the Type II group when compared to the type I-II group which in turn was lesser than type I group. The Mean duration of paralysis also varied among the different groups and was longer in the Type II and Type I-II groups when compared to the Type I group.

Mechanical ventilation rates were equally high in all the groups, with all patients in the type II group requiring mechanical ventilation. Mean duration of mechanical ventilation was longer in the type II and type I-II groups when compared to the type I group.

ENCEPHALOPATHY

Encephalopathy is described as development of altered sensorium with a GCS of less than 13/15 in an un-intubated patient and a GCS of less than 8T/15 in an intubated patient.

We have divided encephalopathy as

1) Early - Develops at admission or within 72 hours of consumption of the organophosphorus compound.
2) Delayed – Develops or persists 72 hours after consumption of the organophosphorus compound.

PATTERN OF EARLY ENCEPHALOPATHY

Early encephalopathy is described as encephalopathy which is present at admission and resolves by 72 hours after consumption of the compound.

The following table 14 describes individual patients with early encephalopathy and their Severity of poisoning assessed by namba scale, GCS at admission, duration of encephalopathy, duration of mechanical ventilation and lowest GCS recorded during hospital stay.

Table 14 Description of individual patient with early encephalopathy

Serial number	Namba score	GCS at admission	Duration of Encephalopathy	Duration of Mechanical Ventilation	Lowest GCS
78	Severe	2T	2	10	2T
12	Severe	7T	3	14	7T
72	Severe	3	1	2	3
32	Severe	3	1	3	3
3	Severe	3	1	10	3
16	Severe	4	1	3	4
55	Severe	4	1	5	4
41	Severe	4	1	4	4
60	Severe	5	1	3	4
66	Severe	6	1	2	4T
50	Severe	6	1	2	6
77	Severe	7	2	37	6
61	Severe	7	2	11	7
1	Severe	8	1	4	7
25	Severe	8	2	5	8
43	Mild	9	1	2	8
71	Severe	9	1	6	9
52	Severe	9	1	3	11
49	Severe	9	1	0	9
53	Moderate	11	1	14	11
70	Severe	11	1	0	11
79	Severe	12	1	2	12
19	Moderate	12	1	0	12

As seen in the tables 14, 23(29.5%) patients out 78 had presented with low sensorium defined as GCS less than 13/15(8T/15 for an intubated patient. 2(8.7%) patients among the patients with early encephalopathy were already intubated elsewhere in a local hospital. 20 patients(87%) required mechanical ventilation for mean ventilators days of 7.5 days. Mean duration of early encephalopathy is 1.26 days. As we can see the requirement for mechanical ventilation was longer than the early encephalopathy duration as patients required mechanical ventilation for muscle weakness. (Relationship between muscle weakness and encephalopathy has been described in the following sections).

PATTERN OF DELAYED ENCEPHALOPATHY

Delayed encephalopathy is described encephalopathy which develops or persists after 72 hours of consumption of the OP compound.

The following table describes individual patients with delayed encephalopathy and their Severity of poisoning assessed by namba scale, GCS at admission, duration of encephalopathy, duration of mechanical ventilation and lowest GCS documents during hospital stay.

Table 15 Description of individual patient with delayed encephalopathy

Serial Number	Namba score	GCS at admission	Duration of Encephalopathy	Duration of Mechanical Ventilation	Lowest GCS
73	Severe	2T	5	11	2T
74	Severe	5	12	11	4T
75	Severe	3	12	15	2T
76	Severe	11	6	22	2T

As seen in table 8, 4 patients developed delayed encephalopathy. Mean duration of delayed encephalopathy was 8.75 days and mean duration of mechanical ventilation was 14.75 days. 3 out 4 patients had lowest GCS recorded as 2T/10.

3 out of 4 patients subsequently returned to normal sensorium and were discharged alive.1 patient was discharged against medical advice, hence the outcome of the patient is not known.

Table 16 Comparison of clinical finding in early and delayed encephalopathy

	Early Encephalopathy	Delayed Encephalopathy
Frequency n (%)	23(29.5%)	4(5.1%)
Namba Mild (%)	1(4.3%)	Nil
Moderate (%)	2(8.6%)	Nil
Severe (%)	20(87.1%)	4(100%)
Mean GCS at admission		
Intubated(SD)	4.5T (3.5)	2T
Range	2T – 7T	Not applicable
Not intubated(SD)	7.14(3.0)	6.33(4.16)
Range	3 – 12	3 - 11
Mean Lowest GCS		
Intubated(SD)	4.3T (2.5)	2.5(1)
Range	2T – 7T	2T – 4T
Not intubated(SD)	7.1(3.2)	None
Range	3 – 12	None
Mean duration of Encephalopathy(SD)	1.26 days(0.54)	8.75 days(3.77)
Range	1 – 3 days	5 – 12 days
Mean duration of mechanical ventilation	7.1 days	14.75 days
Range	2 – 37 days	11 – 22 days

As in the table 16, comparison of early and delayed encephalopathy, the incidence of delayed encephalopathy is much less common when compared to early encephalopathy. The severity of poisoning at admission was similar between the two groups with patients predominantly presenting with features of severe poisoning. Sensorium assessed by Glasgow coma scale at admission was lower in the delayed encephalopathy group when compared to the early encephalopathy and the lowest GCS recorded during the illness also was lower in the delayed encephalopathy group when compared to the early encephalopathy group. The mean duration was longer in the delayed encephalopathy (Mean – 8.75 days) when compared to the early encephalopathy group (mean duration – 1.26 days). The duration of mechanical ventilation was longer in the delayed encephalopathy group (mean duration-14.71 days) as the duration of encephalopathy also longer in this group, when compared to the early encephalopathy group(mean duration – 14.75 days).

In summary, 27 patients (%) had low GCS at admission. Of them, (23/27) % the sensorium normalised within 72 hours (early encephalopathy). However in (4/27)% the sensorium continued to be depressed for a variable duration. It appears that delayed encephalopathy, in patients who have a prior normal sensorium did not occur in the study group.

TEMPORAL PROFILE OF PARALYSIS AND ENCEPHALOPATHY

TEMPORAL PROFILE OF EARLY ENCEPHALOPATHY AND PARALYSIS

The following table 17, compares individual temporal profile of paralysis and encephalopathy with GCS at admission, encephalopathy duration, type of paralysis, paralysis duration, lowest GCS recorded and lowest power in the proximal muscles around the shoulder and hip.

Table 17 Temporal profile of individual patients with early encephalopathy and paralysis

Serial Number	GCS at admission	Duration of Encephalo-pathy	Type of Paralysis	Duration of Paralysis	Lowest GCS	Lowest Power Shoulder-Hip
78	2T	2	Type I-II	10	2T	2 - 1
12	7T	3	Type I-II	9	7T	3 - 3
72	3	1	Type I	1	3	4 - 4
32	3	1	Type I-II	2	3	4 - 4
3	3	1	Type I-II	9	3	3 - 3
16	4	1	Type I	1	4	5 - 5
55	4	1	Type I	1	4	3 - 3
41	4	1	Type I-II	4	4	4 - 4
60	5	1	Type I	1	4	4 - 4
66	6	1	Type I	2	4T	4 - 4
50	6	1	Type I	1	6	5 - 5
77	7	2	Type I-II	38	6	1 - 1
61	7	2	Type I-II	5	7	3 - 3
1	8	1	Type I	2	7	4 - 4

Temporal profile of individual patients with early encephalopathy and paralysis (Table continued)

Serial Number	GCS at admission	Encephalo-pathy Duration	Type of Paralysis	Paralysis Duration	Lowest GCS	Lowest Power Shoulder-Hip
25	8	2	Type I-II	4	8	3 - 3
43	9	1	Type I	1	8	4 - 4
71	9	1	Type I	2	9	4 - 4
52	9	1	Type I	3	11	4 - 4
49	9	1	Nil	0	9	5 - 5
53	11	1	Type II	9	11	2 - 2
70	11	1	Nil	0	11	0 - 0
79	12	1	Type I-II	4	12	2 - 2
19	12	1	Nil	0	12	5 - 5

23(29.5%) patients out of 78 patients had early encephalopathy only. 3(13%) patients did not have any neuromuscular weakness whereas 20 patients had weakness which lasted for varying duration. Mean duration of encephalopathy was 1.26 days with a maximum of 3 days and minimum if of 1 day of encephalopathy. Mean duration of paralysis was 5.45 days.

Mean power in the upper limb was lower limb was 3.3.

TEMPORAL PROFILE OF DELAYED ENCEPHALOPATHY AND PARALYSIS

Table 18 Temporal profile of individual patients with delayed encephalopathy and paralysis

	Early Encephalopathy	IMS	Encephalopathy Duration	Paralysis Duration	Lowest GCS	Lowest power
Patient 1	2T/10	Yes	Day 1 – 10	Day 1 -11	2t/10	UL-2/5 LL-2/5
Patient 2	5/15	Yes	Day 1- 12	Day 1 -12	4T/10	UL-3/5 LL-3/5
Patient 3	3/15	Yes	Day 1 – 12	Day 1- 12	2T/10	UL-4/5 LL-4/5
Patient 4	11/15	Yes	Day 10- 15	Day 1 - 20	2T/10	UL-2/5 LL-3/5

4(5.1%) patients out of 78 patients had encephalopathy which present beyond 72 hours after consumption of OP compound. All four patients had low sensorium at admission and 3 patients had persistent low sensorium which required varying duration of mechanical ventilation.

Mean duration of encephalopathy was 9.75 days and mean duration of paralysis was 13.75 days. All four patients with delayed encephalopathy also demonstrated Type I-II continuum weakness. 3 patients recovered completely and were discharged alive and well while 1 patient was discharged against medical advice, hence the outcome of the patient was not known.

Table 19 Comparison between clinical finding of early and delayed encephalopathy.

	Early encephalopathy	Delayed encephalopathy
Type I paralysis (%)	10 (43.5%)	Nil
Type I – II paralysis (%)	9 (39%)	4 (100%)
Type II paralysis (%)	1 (4.5%)	Nil
No weakness	3 (13%0	Nil
Mean lowest muscle power in Shoulder(SD) Range	3.3 (1.3) 0 – 5	2.75(0.95) 2 - 4
Mean lowest muscle power in Hip(SD) Range	3.3 (1.3) 0 - 5	3(0.81) 2 - 4
Mean duration of paralysis	5.45 days	13.75 days
Mean duration of Encephalopathy	1.26 days	9.75 days

The table 19 above summarises the temporal profile of paralysis among early and delayed encephalopathy.

Entire spectrum of paralysis is seen among the patient with early encephalopathy. Type I paralysis and Type I-II continuum paralysis occurs almost equally accounting for 83% of the patients with paralysis. Type II paralysis is seen in only 1 patient with early encephalopathy. Patients with delayed encephalopathy exhibit only Type II paralysis.

The mean lowest power in the upper limb and lower limb are lower in the delayed in the delayed encephalopathy group when compared to the early encephalopathy.

The two groups mainly differ in the duration of paralysis with duration of paralysis being prolonged in the delayed encephalopathy group. The duration of mechanical ventilation and encephalopathy is longer in the delayed encephalopathy as the patients require prolonged ventilatory support till the sensorium recovers.

PATTERN OF PARALYSIS AND ENCEPHALOPATHY AMONG

INDIVIDUAL ORGANOPHOSPHORUS COMPOUNDS

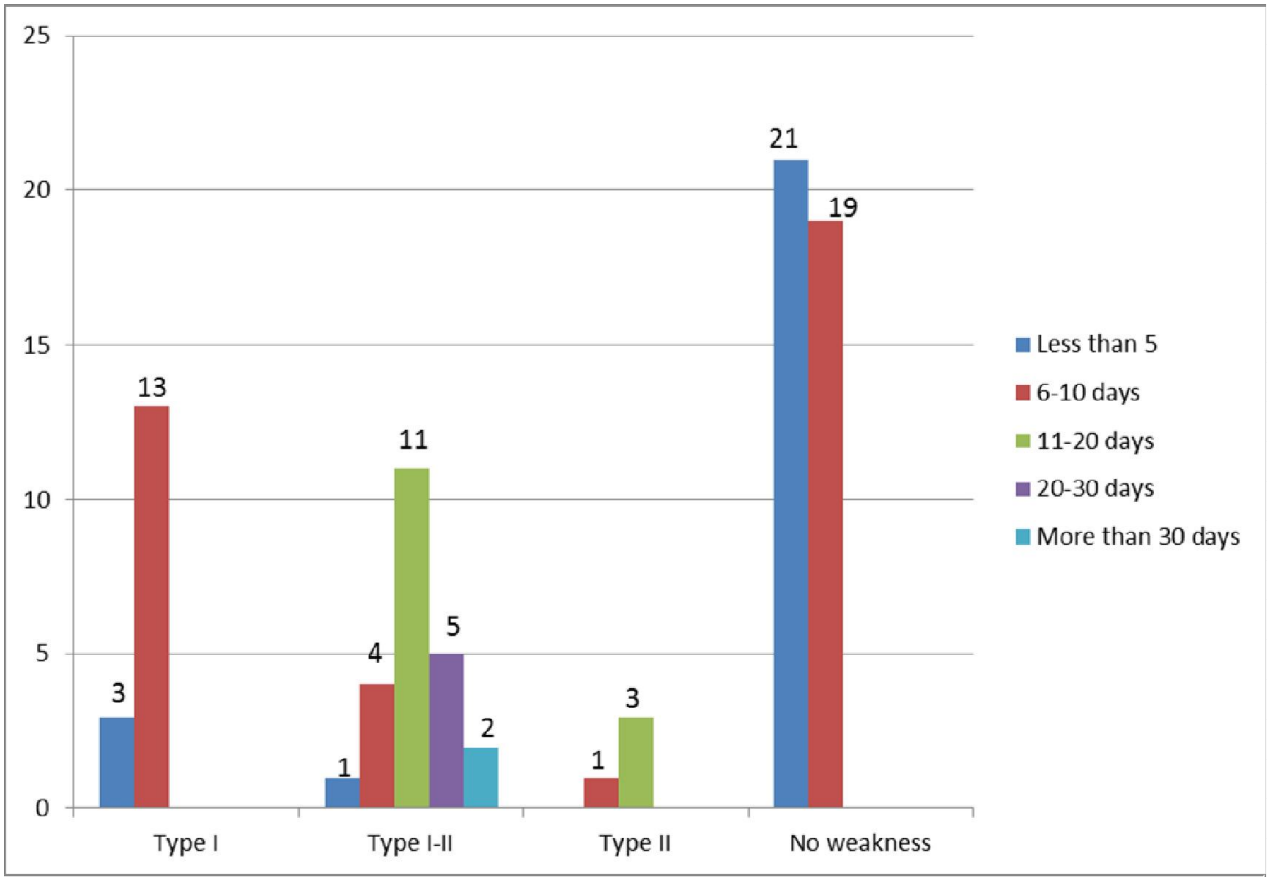
Table 20 - Pattern of Paralysis and encephalopathy with individual OP compounds.

	Quinalphos	Monocrotophos	Profenophos	Chlorpyriphos	Phorate
Frequency	11	10	10	9	9
No weakness (%)	5 (45.5%)	5(50%)	4(40%)	7(77.8%)	5(55.5%)
Type I weakness (%)	3(27.3%)	2(20%)	3(30%)	Nil	2(22.2%)
Type I-II Weakness (%)	3(27.3%)	3(30%)	2(20%)	1(11.1%)	2(22.2%)
Type II Weakness (%)	Nil	Nil	1(10%)	1(11.1%)	Nil
Early Encephalopathy (%)	3(27.3%)	3(30%)	2(20%)	1(11.1%)	2(22.2%)
Delayed Encephalopathy (%)	Nil	Nil	Nil	Nil	1(11.1%)
Mean duration of Paralysis(SD)	6 days (4.2)	9.33 days (5.03)	6 days (5.8)	6 days (4.25)	2 days (1.73)
Mean duration of Encephalopathy	1.25 days	1.67 days	1 day	1 day	4.67days

The above table describes different types of weakness and encephalopathy among 5 most common types of organophosphorus compounds in our study. The rates of different types of paralysis are nearly equal among the different types of compounds. The rates of early encephalopathy seem to be equal among the compounds. The mean duration of paralysis is longer among the patient with monocrotophos and phorate group. From this comparison we can see the incidence of paralysis and encephalopathy are equal among different compounds with the duration of paralysis and encephalopathy prolonged among the Monocrotophos group.

DURATION OF HOSPITAL STAY

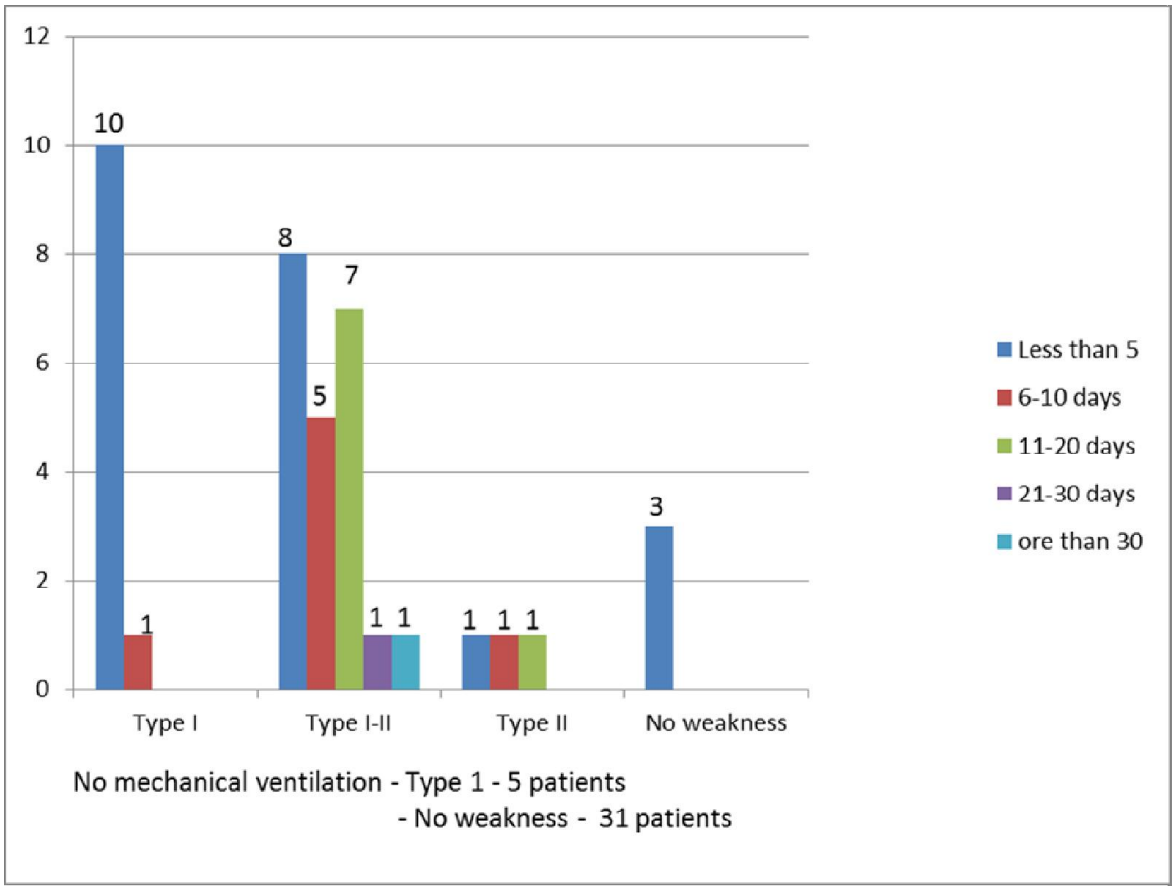
Figure 13 Duration of Hospital stay



Mean duration of hospital stay among patients who had no weakness was 5.6 days(SD-1.6). Mean duration of hospital stay in Type I weakness was 6.75 days (SD-1.39).Mean duration of hospitalisation in Type I-II continuum weakness was 18.09 days(SD-11.78). Mean duration of hospitalisation in Type II weakness 13.75 days(SD-4.5). The results suggest that the presence of paralysis and duration of paralysis prolong the duration of hospitalisation

MECHANICAL VENTILATION

Figure 14 Duration of mechanical ventilation

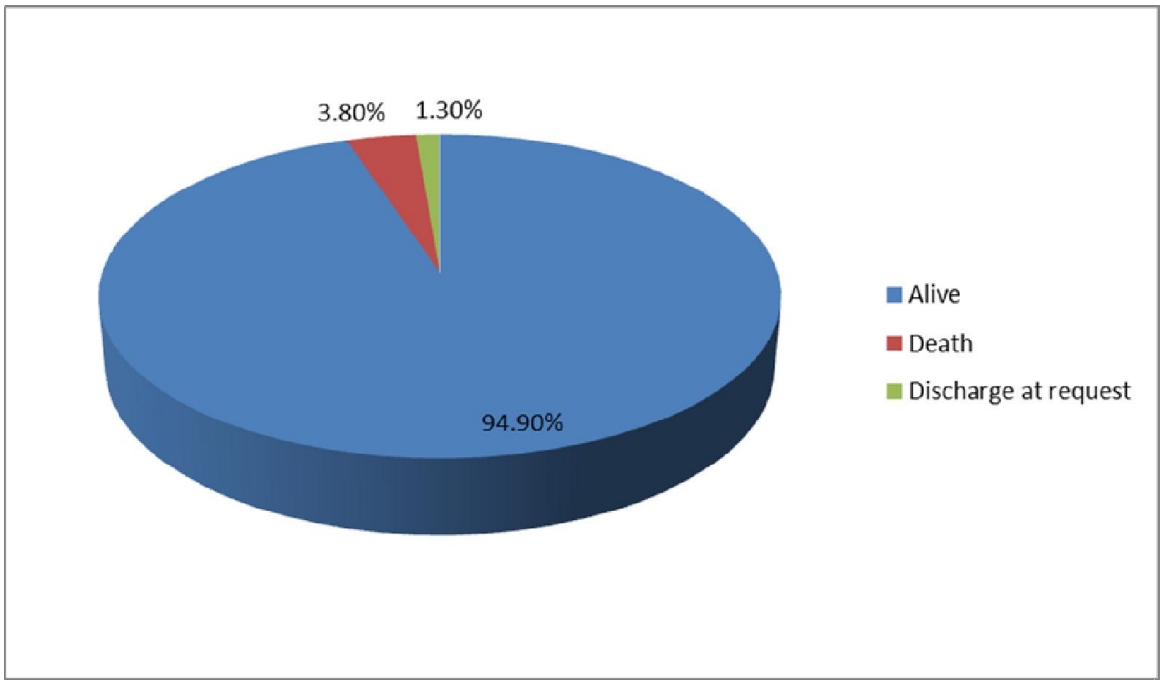


31 patients out of 78 patients with no weakness and 5 patients with Type I weakness did not require any mechanical ventilation. 10 patients with type I weakness, 8 patients with Type I-II continuum weakness, 1 patient with Type II weakness required mechanical ventilation less than 5 days. 1 patient with Type I weakness, 5 patients with Type I-II continuum weakness and 1 patient with Type II weakness required ventilation between 6 to 10 days. 7 patients with Type I-II weakness and 1 patient with Type II weakness required mechanical ventilation

between 11 to 20 days. 2 patients with Type I-II continuum weakness required mechanical ventilation for 22 days and 37 days.

HOSPITAL OUTCOME

Figure 15 Outcome of patients at discharge



74 patients (94.9%) were discharged alive and well. 3 patients were discharged at request and 1 patient died during treatment due to ventilator associated pneumonia and septic shock.

PREDICTORS OF INTERMEDIATE SYNDROME

The predictors of Intermediate syndrome that were assessed in this study are

1) WHO class of compound
2) Type of Compound
3) Neck muscle weakness at admission
4) GCS at admission
5) Namba score at admission
6) Pseudocholinesterase

1) WHO CLASS OF COMPOUND

Table 18 WHO class of compound and Intermediate syndrome

		NO IMS	IMS
WHO CLASS	**I n**	19	9
	%	68%	32%
	II n	22	9
	%	71%	29%
	III n	7	3
	%	70%	30%
Pearson chi-square test – 0.743			

In order to calculate the significance of WHO class of compound, patients with WHO class I and II compound poisoning were considered to have a higher chance of developing IMS. But the difference was not statistically significant.

2) TYPE OF ORGANOPHOSPHORUS COMPOUND

Table 19 – Type of compound and Intermediate syndrome

		No IMS	**IMS**
TYPE	**Dimethyl n**	18	7
	%	72%	28%
	Diethyl n	23	10
	%	69.7%	30.3%
	S Alkyl n	7	4
	%	63.4%	36.6%
Pearson chi-square test – 0.465			

The prevalence of Intermediate syndrome was nearly equal in the different type of compounds (dimethyl, diethyl and s-alkyl) and we did not demonstrate a statistically significant co-relation between the type of compounds and development of IMS.

3) NECK MUSCLE WEAKNESS AT ADMISSION

Table 20 Neck muscle at admission and Intermediate syndrome

		NO IMS	IMS
WEAKNESS	**YES n**	16	21
	%	43.3%	56.7%
	NO n	37	4
	%	90.2%	9.8%
Pearson chi-square test – 0.001			

56.7% of patients who had weakness at admission, went onto to develop IMS compared 9.8% of those who had no muscle weakness at admission. Neck muscle weakness assessed at admission was found to be a risk factor which was significantly associated development of IMS (p=0.001).

4) GLASGOW COMA SCALE

Table 21 Glasgow coma scale at admission and Intermediate syndrome

		NO IMS	**IMS**
GCS	**>/=13 n**	40	12
	>/= 8T %	%	30.4%
	<13 n	13	13
	<8 T %	52.9%	47.1%
Pearson chi-square test – 0.016			

47.1% of patients who presented with low GCS (<13 in non-intubated patients and <8 in intubated patients) went onto develop IMS compared to 30.4% in patients who normal GCS (>13 in non-intubated patients and >8 in intubated patients). Low Glasgow coma scale assessed at admission was found to be significantly associated with development of IMS (p=0.016) and maybe a risk factor for development of IMS.

5) SEVERITY OF POISONING ASSESSED BY NAMBA SCALE

Table 22 Severity of poisoning (Namba scale) and Intermediate syndrome

		NO IMS	IMS
NAMBA SCALE	**LATENT n**	5	0
	%	100.0%	.0%
	MILD n	16	1
	%	94%	6%
	MODERATE n	16	6
	%	72.7%	27.3%
	SEVERE n	16	18
	%	47%	53%
Pearson chi-square – 0.001			

In order to calculate the significance of Namba scale as a risk factor for developing IMS, Latent and mild poisoning were coupled together and were compared with patients with moderate and severe poisoning. No patient with latent OP poisoning and 6% of patients with mild OP poisoning (1 of 16 patients) developed IMS compared to 27.3% of those with moderate and 53% with severe poisoning. Moderate and severe poisoning were significantly more likely to develop IMS than latent and mild poisoning (p=0.001).

6) PSEUDOCHOLINESTRASE

Pseudocholinesterase is continuous variable, hence it was evaluated by Mann-Whitney test to as significance and median.

Table 23 Pseudocholinestrase and intermediate syndrome

	IMS	Frequency	Median	Minimum	Maximum
Pseudocholinestrase	No	53	266	37	10,725
	Yes	25	116	40	3457

The mean Pseudocholinestrase value in patients who developed IMS was 729.42 U/L compared to 3399.87 U/L in those who did not develop IMS and this was statistically significant (p+0.002). A normal BuChE at admission appears to predict that patients will not develop IMS and a low BuChE level appears to a risk factor for development of IMS

MULTIVARIATE ANALYSIS OF RISK FACTORS FOR INTERMEDIATE SYNDROME

The risk factors which were analysed by univariate analysis and the risk factors which had significance of more than 25 % were taken for multivariate analysis.

The following risk factors were assessed by multivariate analysis.

1) Neck muscle weakness at admission
2) Glasgow coma scale at admission
3) Severity assessed by Namba scale
4) Serum pseudocholinesterase levels done at admission
5) Type of Compound
6) WHO class of compound

Table 24 Multivariate analysis of risk factors of IMS.

	Chi-square test	**P value**	**Odd's ratio**	**Confidence interval**	
				Lower limit	Upper limit
WHO class	0.74	0.47	0.67	0.23	1.98
Type of Compound	0.47	0.74	0.84	0.29	2.45
Neck muscle weakness	**0.001**	***0.005***	**7.87**	**1.86**	**33.40**
GCS	**0.02**	0.64	1.38	0.36	5.34
Namba	**0.001**	0.57	1.78	0.25	12.77
Pseudocholinesterase		0.016	0.28	0.10	0.79

The risk factors which were significant in the univariate analysis (GCS, Namba scale and neck muscle weakness at admission) were analysed in the multivariate analysis.

Neck muscle weakness was found to be significantly associated with development of Intermediate syndrome(p – 0.005;OR – 7.87;CI – 1.86 – 33.4). Pseudocholinesterase levels also achieved statistical significance after multivariate analysis (p – 0.016;OR- 0.28;CI – 0.10 -0.790. Glasgow coma scale (p -0.64;OR – 1.38;CI – 0.36 - 5.34) and Namba scale(p – 0.001;OR – 1.78;CI - 0.25 – 12.77) which were significant in the univariate analysis lost their significant in the multivariate analysis.

PREDICTIVE SCORING SYSTEM

The Predictive scoring system was formed from a previous study which evaluated the risk factors for intermediate syndrome.

Components of Predictive scoring system: -

Table 25 Predictive score system

Risk factors	Maximum score	Minimum score
Muscle weakness at admission	4	0
Severity assessed by Namba	3 / 2	1
Glasgow coma scale at admission	2	1
WHO class of compound	2	1
Type of compound	2	1

The correlation between the scores and development of intermediate syndrome was done using receiver operating characteristics curve and results are as follows.

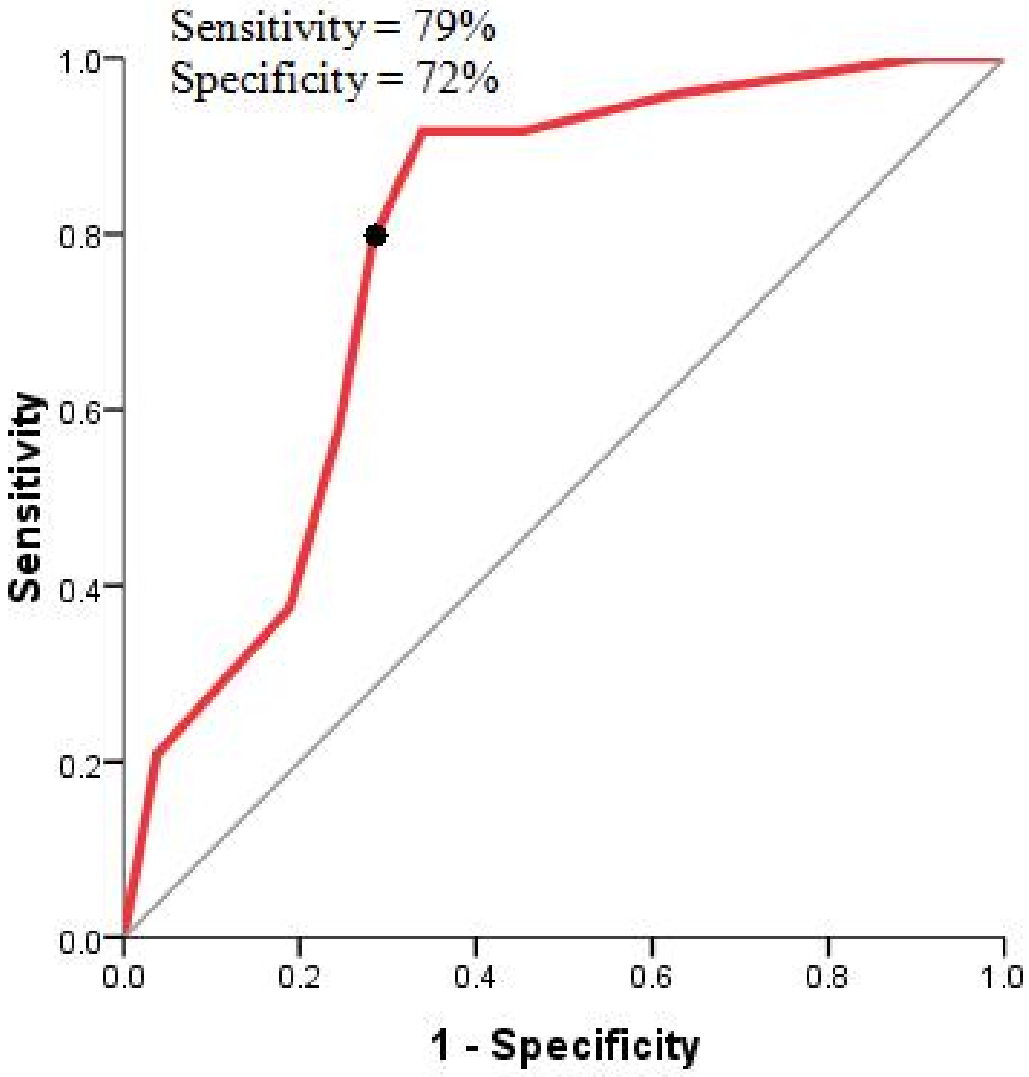


Figure 16 ROC curve - Predictive socring system

Area under the curve – 0.784

Standard error – 0.053

Confidence interval – 0.68 to 0.88

Table 26 Sensitivity and Specificity for predictive score

Score	Sensitivity	Specificity
2.00	1.000	0.000
3.50	1.000	0.019
4.50	1.000	0.094
5.50	0.958	0.377
6.50	0.917	0.547
7.50	0.917	0.660
8.50	0.875	0.679
9.50	0.792	0.717
10.50	0.583	0.755
11.50	0.375	0.811
12.50	0.208	0.962
14.00	0.000	1.000

The area under the curve was calculated to be 0.784, which indicates the test being evaluated is a fairly good test for assessing patients who may develop intermediate syndrome. The sensitivity and specificity for individual scores were calculated by plotting the area under the curve and the values are presented in the table above.

The test performs best for a score of 9.5 with sensitivity of 79.2% and specificity of 71.7%.

In order to test the scoring system the score with best sensitivity and specificity and two more scores – 1 score above the best score and 1 score below the best score was taken and the individual Sensitivity, specificity, positive predictive value, negative predictive value, likelihood rations and post-test probabilities were calculated.

Table 27 Post-Test probability for individual predictive scores

Score	Sensitivity	Specificity	PPV	NPV	Likelihood ration	Post-test Probablity
8.5	87.5	67.92	55.26	92.31	2.73	55%
9.5	79.17	71.70	55.88	88.37	2.8	56%
10.5	58.33	75.47	51.85	51.85	2.38	52

Table 28 Cross tabulation of predictive score and intermediate syndrome

Score	3	4	5	6	7	8	9	10	11	12	13
IMS-Yes	0	0	1	1	0	1	2	5	5	3	6
IMS-No	1	3	15	10	6	1	2	2	3	8	2

The predictive score at a score of 8 has a Sensitivity and specificity of 87.5% and 67.9% and Positive and negative predictive value of 55.2% and 92.3%. Among the patients in this study, 55% (22/40) with admission score ≥8 developed IMS compared to 5% (2/37) with score <8. For a patient to have a score of 8 based on clinical criteria, they would have neck muscle weakness (score of 4), moderate or severe poisoning (score of 2 or 3) with GCS <13 (score of 2). A combination of all these clinical criteria, a patient has 55.2% likelihood of developing IMS. In the absence of any or all of these, the likelihood of developing IMS falls to 5%.

Hence with high sensitivity and high negative predictive value at a cutof score of 8, the scoring system can be a good tool to rule out patients who will not develop intermediate syndrome.

Discussion

DISCUSSION

CLINICAL PROFILE AT ADMISSION

78 patients were enrolled in our study to assess the temporal profile of encephalopathy and paralysis in patients who present with acute organophosphorus poisoning.

Incidence of Intermediate Syndrome

The incidence of Intermediate syndrome in our study was 33.4%. This rate was similar to earlier reports of incidence of intermediate syndrome reported from our institution that have varied from 37.5% (Lovely et al) and 47% in a study done by Peter et al.(10). However the incidence of Intermediate syndrome in published literature had been varied. , In contrast in a study done by Jayewardene at al in Sri Lanka reported the incidence of 11.5%. This may have been due to restriction of WHO class I compounds in Sri Lanka(20). However other studies from India have also reported lower incidences (Indira et al reported 17.6% incidence).(21)

Background characteristics and clinical profile

The background profile of OP poisoning in this study was similar to earlier descriptions, affecting the young adults (between 15-30 years), predominantly men and chiefly due to deliberate self harm (10)(22). The majority of patients were moderate to severely poisoned reflecting the high rates of cholinergic symptoms of salivation, vomiting and altered sensorium.Similarly three-fourth of the patients had received treatment in a local hospital before presenting to our hospital including gastric lavage, atropine and oximes reflecting the referral pattern of severely poisoned patients to our hospital.

Type of Organophosphorus poison consumed

As in earlier studies we were able to identify the OP compound in the majority of patients based on the history and the poison container brought with the patient. 88% patients had poisoning with an identified organophosphorus compound and the most common consumed compounds were Quinalphos (n=11, Monocrotophos (n=10) and Profenophos (n=10), Chlorpyriphos (n=9), Phorate (n=9). Four of the five most commonly consumed poisons were Class I and Class II compounds.. The distribution of type of compounds (Dimethyl-32%, Diethyl-52%) and WHO class (Class I-40.5%, Class II-45%) of compound among the identified were represented equally. These results are similar to the study by Lovely et al and indicate the predominant poison with highly toxic Class I and Class II OP compounds and the free access of these compounds in the Indian market and to the local community. The identification of compounds in the majority of case made it possible for us to study the association between specific compounds and the development of Intermediate syndrome.

Clinical profile of muscle paralysis in organophosphate poisoning

About half the patients did not develop any muscle paralysis. Of the other half, 20.5% developed early paralysis (Type I paralysis) and about 33.3% developed early paralysis that persisted beyond 72 hours (Type I and Type II paralysis continuum). Only a minority of 4 patients developed new onset weakness after 72 hours (pure Type II paralysis).

The analysis of the clinical features of muscle paralysis between Type I and Type I and II paralysis continuum in our study suggests that the main difference between these two is the severity of weakness and the duration of weakness.

These confirm the concept suggested by Mathew(14), Avasthi(19) and Jayawardane et al(20), that Type I and Type II paralysis are not separate clinical entities but that there is a continuum of the same paralysis. Patients with mild poisoning do not develop any paralysis. Patients with moderate to severe poisoning may develop muscle paralysis which recovers (Type I paralysis) or may continue to be paralysed for a longer period after the cholinergic signs improve (Type II paralysis). The chief determinant of whether a patient develops Type I or Type II paralysis appears to be the severity of poisoning.

Risk factors for the development of intermediate syndrome

Relationship between Type of OP compound, WHO class and specific compounds and intermediate syndrome.

In our study we found that the rates of IMS did not vary between WHO compound class, dimethyl and diethyl compounds and between most commonly ingested compounds. There was no statistical correlation between the type of compound and development of intermediate syndrome.(p value – 0.47) and between WHO class and development of Intermediate syndrome.(p value – 0.74).) This is in contrast to earlier studies have also shown that poisoning with organophosphorus compounds belonging to WHO class I and II had a higher chance of developing intermediate syndrome (2). Studies by Peter et al demonstrated that dimethyl compounds had a higher chance of developing intermediate syndrome (10). Senenayake also found association between specific compounds and the development of intermediate syndrome in his initial descriptions(23).

The results of our study suggest that IMS is class independent and compound independent complication of acute organophosphorus poisoning.

Severity of poisoning and the development of intermediate syndrome

In our study neck muscle weakness assessed at admission was found to be a significant risk factor for development of intermediate syndrome. (p – 0.005; CI 1.8 to 33.4). Sensorium assessed by Glasgow coma scale at admission and severity assessed by Namba scale were significantly associated with the development of intermediate syndrome.(p – 0.016 and p value – 0.001 respectively). Similar conclusions were drawn from a study done by Indira et al and she had described age more than 45 years, neck muscle weakness and poisoning severity score of more than 2 was associated with higher chance of developing respiratory failure.(21)

Pseudocholinestrase levels measured at admission correlated well with development of intermediate syndrome (p value – 0.02). Although the results for pseudocholinestrase as a risk factor for development of IMS are varied, Avasthi et al and Shailesh et al, in their studies have demonstrated an association between the same. Hence our study suggests that severe inhibition of pseudocholinesterase should provide a clue to the clinician to carefully monitor patients for the development of IMS (22)(19).

Although GCS and severity assessed by Namba scale had significant association with the development of IMS, after logistic regression and multivariate analysis, they failed to show significant correlation. This finding could be explained by the fact that the two risk factors may be related and hence the statistical significance is lost when combined in the multivariate analysis. The inter-relationship between parameters severity of poisoning, low GCS and neck muscle may be confounding their individual relation to IMS in a logistic regression analysis.

Nevertheless neck muscle weakness assessed at admission, GCS at admission and Severity of poisoning assessed by Namba scale can individually be used as a risk factor for prediction of intermediate syndrome in patients with acute organophosphorus poisoning. The analysis

seems to suggest that the most important pathogenetic factor leading to the development of IMS is a high poison load that causes central and peripheral Acetylcholinesterase inhibition manifesting with features of severe poisoning (cholinergic signs), low GCS and neck muscle weakness. The IMS appears to be class and compound independent phenomenon related to the severity of poisoning and the severity of Acetylcholinesterase inhibition.

CENTRAL AND PERIPHERAL NEUROMUSCULAR MANIFESTATIONS OF OP POISONING

Two most common complications of organophosphorus poisoning are muscle weakness and encephalopathy. Although various studies have described intermediate syndrome but there have been no prospective studies which have described them together. Peter et al in a retrospective study described delayed encephalopathy as altered sensorium developing after 72 hours of consumption of the toxin. In our study, early paralysis (Type I weakness) was seen in 16(20.5%) patients. Delayed paralysis (Type I-II and Type II weakness) was seen 26(33%) patients.

Early encephalopathy was seen in 23 patients (29.5%) and delayed encephalopathy, that is low sensorium developing after 72 hours after consumption or persisting low sensorium beyond 72 hours, was seen in 4(5%) patients. Early encephalopathy has been described in the history of acute organophosphorus poisoning by Wadia et al and it is well known that early encephalopathy can be caused by multiple factors such as toxic delirium secondary to the organophosphorus compound, central receptors dysfunction due the toxin or maybe secondary to atropine toxicity itself. Early encephalopathy has good response to treatment with atropine and resolves within a few days. In our study, patients with early encephalopathy had a mean duration of 1.26 days for recovery of altered sensorium and required mechanical

ventilation for a short duration as a supportive treatment during the recovery period (Mean ventilator days – 7.5days). The majority of patients with early encephalopathy had early muscle weakness (10(43.5%) patients with early encephalopathy among 23 patients who had early encephalopathy also had early type I paralysis).

Patient who had persisting low sensorium beyond 72 hours required prolonged ventilation (mean ventilator days – 14.75 days). All four patients who developed delayed encephalopathy also developed muscle weakness of varying duration (duration of muscle weakness – 13.75 days). The delayed encephalopathy and muscle weakness were coincident and parallel which suggests that similar mechanisms may be involved in both clinical phenomena. Hence we propose a similar mechanism which mediates intermediate syndrome maybe involved in patients who develop delayed encephalopathy.

These results appear to suggest that encephalopathy and muscle weakness are coincident manifestations of the same syndrome. There are three patterns of the relationship between encephalopathy and muscle weakness. In the early phase of severe poisoning, most patients have encephalopathy and muscle weakness. In the first pattern, encephalopathy and muscle weakness both recover in 72 hours (40%) which takes place in Type I paralysis. In the second pattern, encephalopathy recovers but the muscle weakness persists (40% of patients) which takes place in Type II paralysis. In third pattern which occurs in a minority of patients encephalopathy and muscle weakness persist and recover together, which is the Type II paralysis (IMS) with encephalopathy. We therefore suggest that the term, Delayed organophosphate encephalopathy (DOPE) (16)or CNS intermediate that has been proposed in earlier studies of encephalopathy may not be appropriate, as this syndrome appears to be part of the intermediate syndrome rather than a separate clinical syndrome. We suggest instead the term Intermediate-encephalopathy syndrome (IMES), where a minority of patients with IMS

have persisting encephalopathy with potential for good neurological recovery. Just as Type I and Type II paralysis (IMS) appear to part of continuum of paralysis, similarly early and delayed encephalopathy also appear to be a continuum of low GCS and the paralysis invariably occurs as part of the entire syndrome.

Probable mechanism of Encephalopathy – A hypothesis

Early encephalopathy is mediated by toxic effects of the organophosphorus compound and the dysfunction caused in the synapses in the central nervous system receptors (muscarinic and nicotinic receptors) and the altered sensorium responds well to treatment with atropine. On the other hand, atropine has no effect on delayed encephalopathy. Hence the mechanism of delayed encephalopathy must be a unique process and may be due to persistent inhibition of nicotinic receptors or downstream events at the cellular level.

In our study we have demonstrated that encephalopathy and persistent neuromuscular weakness are coincident in patients with acute organophosphorus poisoning and part of the same syndrome. Numerous mechanisms have been postulated for development of intermediate syndrome. Role of acetylcholinesterase inhibition and excessive stimulation by acetylcholine in the neuronal junction in the peripheral as well as central neuronal junctions have been studied in human and animal models.(24) Inhibited acetylcholinesterase 87% in striatum, 67% in hippocampus, 58% in cerebellum in rats that have been poisoned with monocrotophos, Hence the excessive and prolonged suppression of acetylcholinesterase enzyme in the central neuronal junctions may lead to the persistent altered sensorium.

The role of oxidative stress has been implicated in the progression of type I paralysis to type II paralysis and severely poisoned patients have a higher degree of oxidative stress and hence have higher chance of developing type II paralysis(25)(26). In our study we have seen that patients who present early encephalopathy the sensorium remains depressed in certain individuals, which parallels the progression of Type I paralysis to Type I-II continuum paralysis. In the rat model of monocrotophos poisoning significant lipid peroxidation and antioxidant enzymes were induced 8h after poisoning, directly correlated to high acetylcholinesterase inhibition (>67%) in all areas of the brain. Recovery from monocrotophos poisoning was associated with absence of lipid peroxidation in the brain although acetylcholinesterase inhibition persisted. In this study it was suggested that neurotoxicity of monocrotophos poisoning is characterized by oxidative damage in regions of the brain that exhibit high acetylcholinesterase activity and severe acetylcholinesterase inhibition and that recovery from poisoning is associated with prolonged induction of antioxidants that protect against oxidative damage. Whether oxidative stress plays a role in the mechanism of persisting low sensorium is a hypothesis which needs to be considered and further studies are needed.

Role of muscle injury and post synaptic structure have been postulated in the development of intermediate syndrome.(27)(28) In a study published in our institution, muscle enzymes were enzymes measured serially and it was observed that muscle injury was present at admission and it peaked at 5 days and decreased over the next 5 days.(14) The temporal profile of encephalopathy and paralysis seen in our study parallels a similar course, hence the role of

post synaptic structures acting at a sub-cellular level should be considered in the mechanism of persistent encephalopathy.

Inhibition of mitochondrial ATP synthase, decreased mitochondrial uptake of calcium and increased levels of nitric oxide with altered mitochondrial bioenergetics has been implicated in muscle paralysis in rat model of monocrotophos poisoning. (29) Energy is critical to muscle and it has been suggested that increased demand for energy and failure of energy supply may underlie muscle weakness in Intermediate syndrome. The brain too requires high energy levels. Since muscle weakness and encephalopathy occurs together and parallel each other, it is likely that there are similar mechanisms that operate downstream of acetylchoinesterase inhibition. Whether there are similar mechanisms to those that occurs in muscle weakness that operate in the brain, leading to ATP synthase inhibition and increase in the nitric oxide levels causing persistent encephalopathy is a possible direction for further study.

In our study we have demonstrated that all patients who developed delayed encephalopathy also developed intermediate syndrome but the frequency of delayed encephalopathy was seen much less common than intermediate syndrome.(Incidence of Intermediate syndrome – 33.3% and Delayed encephalopathy - 5.1%). The same observation was made by Peter et al when they had described delayed onset encephalopathy(16). Although the mechanisms of persistent encephalopathy are still unknown, there seems to be an underlying mechanism which makes it a rarer manifestation of acute organophosphorus poisoning when compared to type 2 paralysis. As we have proposed earlier in the discussion that intermediate syndrome and persistent encephalopathy might have a similar mechanism, there might a protective factor which prevents persistent encephalopathy from occurring. Animal studies show that induction of anti-oxidant mechanisms and cytoprotection may determine central nervous

system recovery after monocrotophos poisoning. We hypothesise that there is a failure of a central cytoprotective mechanism that leads to persistent encephalopathy.

In summary our hypothesis is that persistent acetylcholinesterase inhibition underlies both the intermediate syndrome and encephalopathy syndrome. Mechanisms similar to those that occurs in intermediate syndrome in muscle of oxidative stress and altered mitochondrial bioenergetics may also occur in the brain leading to encephalopathy. The failure of central antioxidant and cytoprotective mechanisms may lead to persistent encephalopathy in a minority of patients. This hypothesis offers direction for further research work into the mechanisms of the Intermediate-Encephalopathy syndrome.

NOTE ON PREDICTIVE SCORING SYSTEM

Intermediate syndrome is the most common complications and till date there is no effective treatment nor a tool to predict which patient will develop the complication. As the complication can arise 24 to 96 hours after the toxin consumption all patients with acute organophosphorus poisoning are observed in the hospital for a minimum of 5 days before discharge.(30) Studies have been conducted to predict the mortality associated with acute organophosphorus poisoning. Numerous studies have assessed generic scoring system such as International Program on Chemical Safety Poison Score (IPC PSS), Glasgow coma scale(31), Acute Physiology and Chronic Health Evaluation (APACHE) , Mortality Prediction Model (MPM) II , Simplified Acute Physiology Score(SAPS) II and Poisoning Severity Score (PSS)(32) to predict early neck muscle weakness which help in identifying patients who may require respiratory failure and mortality among organophosphorus poisoning patients. A score of above 2 in the IPC PSS and a low GCS can predict early

respiratory failure,(21) In a retrospective study done, APACHE II score and SAPS II score performed better than PSS and has been suggested to predict mortality in patients with acute organophosphorus poisoning. But in our study we have developed a predictive tool which can assist in emergency triage of patients to predict patients who have a lower chance of developing intermediate syndrome and can be managed safely in the ward or probably can be discharged from the ward earlier than 5 days.

Although numerous tools have been assessed for mortality prediction, this is the first time a tool for prediction on intermediate syndrome has been formulated. The predictive tool included sensorium assessed by Glasgow coma scale, Severity of poisoning assessed by Namba scale, type and WHO class of compound and neck muscle weakness assessed at admission. The predictive score performed well with area under the curve of 0.784 and sensitivity and specificity of 79% and 72% respectively. The positive predictive value negative predictive values were 56% and 92% respectively.

The predictive tool has a high sensitivity and negative predictive value, hence the tool can be used a screening tool at triage to decide on admission of the patient. Patients with low scores on the prediction role (less than 8) are at low risk of IMS and can be managed in the ward and patients with higher scores (8 or more) and have a 50% risk of developing IMS and require intensive monitoring in an ICU setting. This tool requires validation in a prospective study.

In our study, we also found that type of compound and WHO class of compound did not achieve statistical significance and the predictive tool does not utilise the entire range of the other risk factors as well. Hence if the risk factors (type and WHO class of compound) were removed from the scoring system and neck muscle weakness (MRC grade 1-5), Namba scale (Latent, mild, moderate, severe) and Glasgow coma scale(GCS 3-15) were represented as a

continuous variable, the test might yield better results. This provides an area for further work to develop a reliable clinical prediction rule.

Limitations

LIMITATIONS OF THE STUDY

Our study which looks at temporal relationship between peripheral muscular weakness and central encephalopathic manifestations was planned on 169 patients. But the final sample size was restricted to 78 patients due to time constraints. Hence the risk factor assessment maybe limited due to the smaller sample size.

The assessment of neuromuscular weakness and sensorium done among patients who were mechanical ventilation were done after stopping sedation for a minimum of 4 to 6 hours. Hence the assessment may have overestimated patients with encephalopathy.

SUGGESTIONS AND FUTURE DIRECTIONS

1) The predictive scoring system formed in this study can be further validated in a prospective study.
2) The predictive score formed in this study can be further refined if the components such as Namba scale, neck muscle weakness (MRC grade) and Glasgow coma scale are used as a continuous variable.
3) Further studies are required to understand the role of acetylcholinesterase inhibition, oxidative stress, altered mitochondrial bioenergetics and cytoprotection in encephalopathy in acute organophosphate poisoning

Conclusion

CONCLUSION

1) The Incidence of Intermediate syndrome observed in this study is 33.3%.
2) The risk factors for the development of intermediate syndrome identified in this study were: neck muscle weakness at admission (OR -7.87;CI – 1.86 - 33.4), sensorium assessed by Glasgow coma scale (OR - 1.38;CI – 0.36 -5.43) and severity of poisoning assessed by Namba scale(OR – 1.78;CI - 0.3 - 12.8). We have also observed that the type of compound, WHO class do not influence the occurrence of intermediate syndrome. The observations seen in our study suggests that the most important determinant of intermediate syndrome is the poison load, acetylcholinesterase inhibition and the resulting severity of poisoning.

3) Based on the risk factor analysis we propose a scoring system to predict the occurrence of Intermediate syndrome with sensorium assessed by Glasgow coma scale (maximum score – 2), Severity of poisoning assessed by Namba scale(maximum score – 3), type of compound(maximum score – 2), WHO class of compound(maximum score – 2) and neck muscle weakness(maximum score – 4). A score of < 8 is associated with a low risk of development of intermediate syndrome (area under the curve of 0.784 and sensitivity and specificity of 79% and 72% respectively). The positive predictive value negative predictive values were 56% and 92% respectively. The prediction score can be used to screen patients in accident and emergency to triage patients who can be shifted to the ward and discharged earlier and those who require intensive care.

4) Three patterns of muscle paralysis were identified in this study. About half the patients did not develop any muscle paralysis. 20.5% developed early paralysis (Type I paralysis); 33.3% developed early paralysis that persisted beyond 72 hours (Type I and Type II paralysis continuum); 4 (5.1%) patients developed new onset weakness after 72 hours (pure Type II paralysis). The only distinguishing features between Type I and Type II paralysis were the severity of weakness and the duration of weakness which were greater in Type II paralysis. These results support the concept of a Type I Type II paralysis continuum.

5) Early encephalopathy was seen in 23 patients (29.5%) and delayed encephalopathy, that is low sensorium developing after 72 hours after consumption or persisting low sensorium beyond 72 hours, was seen in 4 patients (5%). Patients who had developed delayed encephalopathy had low sensorium at admission, hence we have observed the early and delayed encephalopathy to be a spectrum disorder.

6) Three patterns of the relationship between encephalopathy and muscle weakness were observed in our study. In the early phase of severe poisoning, most patients have encephalopathy and muscle weakness. In the first pattern, encephalopathy and muscle weakness both recover in 72 hours (13%). In the second pattern, encephalopathy recovers but the muscle weakness persists (13% of patients). In third pattern which occurred in 4(5%) patients encephalopathy and muscle weakness persist for > 72 hours and recover together. The results suggest that encephalopathy and muscle weakness are closely inter-related phenomena both in early paralysis (Type I

paralysis) and delayed paralysis (Type II paralysis/intermediate syndrome). Based on the results we suggest that the delayed encephalopathy be referred to as intermediate-encephalopathy syndrome rather than Delayed organophosphate encephalopathy (DOPE). Although patients with persistent encephalopathy require prolonged ventilation, the neurological recovery and prognosis is good.

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Annexure I - **PROFORMA FOR THESIS:** Serial number:

GENERAL INFORMATION

1. Patient name:
2. Patient ID:
3. Age:
4. Sex: 1.Male / 2.Female
5. Marital status: 1.married / 2. Single / 3. Others
6. Education: 1.Uneducated / 2.Educated
7. Profession: 1.Unskilled/2.Semi-skilled/3.Skilled

COMPOUND

8. Compound identified: Yes / no
9. Compound name:
10. Method by which compound identified: Name given by patient/leaflet/bottle brought
11. Type of compound : 1. Dimethyl / 2. Diethyl / 3. Others
12. Percentage of compound :
13. Compound quantity(volume):

DETAIL REGARDING INGESTION

14. Time and date of consumption:
15. Time and date of First medical contact:
16. Time and date of arrival ay CMC:
17. Treatment given outside : 1. Skin decontamination / 2.Induced Emesis / 3. Gastric Lavage/ 4. Atropine / 5. PAM / 6.Intubation
18. Toxidrome: 1. Salivation / 2. Lacrimation / 3. Urination / 4. Defaecation / 5. Vomiting / 6.Seizures / 7. Breathlessness / 8. Fasciculations / 9.Altered sensorium
19. Severity of poisoning by Namba scale: Mild/Moderate/Severe

CLINICAL FEATURE – ON ADMISSION IN E&D

20. GCS at presentatation:
21. Pupils size: PINPOINT / DILATED/ NORMAL (2-5MM)
22. Pulse rate at presentation:
23. Blood pressure at presentation:
24. Respiratory rate at presentation:
25. Saturation at presentation:
26. Neck muscle weakness: Present / Absent
27. Fasciculation : Present / Absent
28. Limb muscle weakness: Upper limb and lower limb

DATE										
29)GCS										
30)Heart rate										
31)Blood pressure										
32)Toxidrome										
33)Ptosis(1.Yes/2.no /3.others										
34)Facial muscle weakness(1.Yes/2.No /3.Others)										
35)Extra-ocular movements(1.Present /2.Absent)										
36)Power-Shoulder										
37)Power-Elbow										
38)Power-Hip										
39)Power-knee										
40)Power-Neck(Neck muscle weakness)										

41)Tone-Upper limb										
42)Tone-Lower limb										
43)Single breath count/FVC/Paradoxical respiration	.									
44)Reflex-Biceps										
45)Reflex-Knee										
49)Reflex-Plantar	.									
50)Fever(Fahrenheit)										
51)Time since last sedation:										
52)Atropine dose per day:										

53. Total duration of admission:

54. Total duration of mechanical ventilation(if applicable):

55. Outcome of patient: 1)Discharged and alive 2)discharged at request 3)Death

56. Comments:

SUMMARY

1. SERIAL NO
2. COMPOUND
3. TIME INTERVAL BETWEEN INGESTION AND FHC:
4. PARALYSIS: Type I paralysis/Type I-Type II paralysis (IMS) continuum/Type II paralysis alone (IMS)
5. DURATION OF PARALYSIS: Day ___ to Day ___.
6. MOST SEVERE PARALYSIS: Muscle weakness grade in upper ___ / lower limb ___.
7. LOWEST SCORE OF GCS: Day ___ to Day ___.
8. LOWEST SCORE OF GCS:
9. INTERMEDIATE SYNDROME – PRESENT / ABSENT
10. CENTRAL NERVOUS SYSTEM INVOLVEMENT – PRESENT / ABSENT
11. PREDICITIVE SCORE

a) Neck muscle weakness	4 / 0	d)Type	2 / 1
b) Namba scale	3 / 2 / 1 / 0	e)Class	2 / 1
c) GCS	2 / 1	TOTAL	-

ANNEXURE II - PATIENT INFORMATION SHEET :

Scoring system to predict the development of Intermediate syndrome in patients with acute organophosphorus poisoning.

This study is to learn more about organophosphorus poisoning and its complications like weakness of muscles and altered sensorium following poisoning. Organophosphorus poisoning is very common problem we face in our region but still we still do not have complete details about its common complications and how to recognize patients who may develop these complications. By undergoing this study you are helping us to understand organophosphorus poisoning. This may help future patients by improving the treatment offered to them.

Participating in the study is entirely voluntary and you can decide to withdraw from the study at any point in time. This will not affect the treatment you will be undergoing in this hospital.

Participating in the study includes signing a consent form and some additional tests:

Electromyography(to assess your muscle function using a standard EMG machine which is safe and is being used regularly in our hospital).

The subject will be examined daily by routine clinical methods as done by your treating doctor. This will not cause any added discomfort to the patient.

As you can understand none of these tests involves any threat to life of the participant and will be mostly painless.

The information obtained in this study will be maintained confidential and the records will be accessed only the study investigators.

If at any point if you have any clarification you can contact me

(Contact Address:

Dr. Nirmal Raj Francis

Phone number : 09994393385

Department of General Medicine Unit – 1

Christian Medical College, Vellore

Tamil Nadu-632009)

ANNEXURE III – PATIENT CONSENT FORM

Scoring system to predict the development of Intermediate syndrome in patients with acute organophosphorus poisoning.

PATIENT CONSENT FORM

Study Title: Temporal profile of central and peripheral neuromuscular features of acute Op poisoning.

Subject's Initials: _____ Subject's Name: _____

Date of Birth / Age:_____

Please initial box

(Subject)

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions. [ ]

(ii) I understand that my participation in the study is voluntary and that I am

free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

(iii) I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access.

However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s) [ ]

(v) I agree to take part in the above study. [ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable Representative:_____

Date: _____/_____/_____

Signatory's Name: _____

Signature of the Investigator: _____

Date: _____/_____/_____

Study Investigator's Name: _____

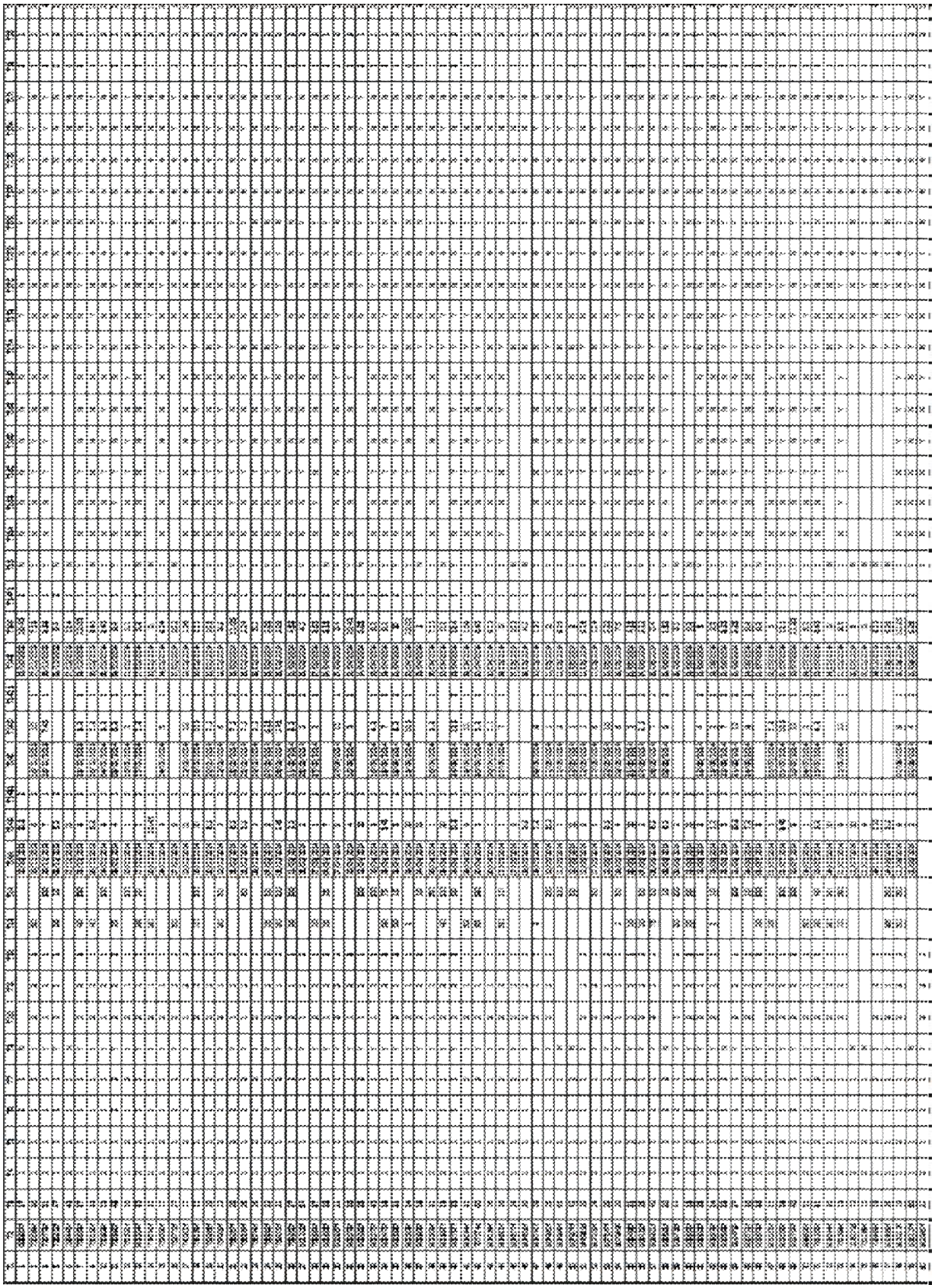
Signature of the Witness: _____

Date:_____/_____/_____

Name of the Witness: _____

ANNEXURE IV – LIST OF TABLES AND FIGURES

ANNEXURE V – DATA SHEET



ANNEXURE V – DATA SHEET

T21	T22	T23	T24	T25	T26	T27	Complaint	T29	T39A	T35	T37	T28	T29	T33	T38B1	T33A	T38	T30	T31	T32	T34	T35	T38	T38A	T39	T40	T41	T42	T43	T44	T45	T46	T47	T48	T49	T50
50	60	30	18	97	Y	Y	0	zerofertfo	8		10/10/2013 10/10/2013	6	4	1	2	41577.00	41559.00	1	240	839	4	4	8		Y	41597.00	41599.00	N	4	2	1	2	1	9	N	185
142	130	100	28	93	N	Y	9	zerofertfo	3		30	20	0	3	5	41595.00	41559.00	1	240	839	4	4			Y	41597.00	41599.00	N	4	2	1	2	1	10	N	80
84	110	60	18	33	Y	N	5	micrototipol	15		26/11/2013 26/11/2013	16	10	2	9	41634.00	41632.00	1	45	158	3	3	3		Y	41637.00	41632.00	N	4	3	2	2	2	13	N	104
118	120	70	24	96	N	N	5	micrototipol	15			7	0	4				1		250					N			N	0	0	1	2	2	5	N	193
116	150	90	20	100	N	N	0		15			7		4				1		100					N			N	0	0	1	1	1	3	N	5384
122	130	80	32	94	N	N	9	zerofertfo	14			9	4	1	3	41630.00	41638.00	1	90	245	4	4	14		N			N	4	3	1	1	1	10	N	94
124	120	80	40	94	Y	N	11	triacaphos	15			20	14	2	10	41634.00	41279.00	1	60	165	3	3		8t	Y	41637.00	41279.00	N	4	3	1	2	1	11	N	105
125	120	80	24	98	N	N	8	phosite	15			4	0	4				1	90	345					N			N	0	1	1	2	1	5	N	1787
110	150	90	26	96	N	N	10	aunalpho	15			7	0	4	0			1	150	280	5	5			N			N	0	2	1	2	1	6	N	179
132	110	60	30	91	Y	N	5	micrototipho	15	7	10/03/2014 13/03/2014	27	14	2	9	41649.00	41657.00	1	60	730	3	3		7	Y	41652.00	41657.00	N	4	3	2	2	2	13	N	40
134	300	60	22	95	N	N	5	micrototipol	15			6	0	4	0			1	30	270	5	5	15		N			N	0	2	1	2	2	7	N	165
112	300	60	18	98	N	N	3	limethoat	15			6	0	4	0			1	15	15	5	5			N			N	0	1	1	2	2	6	N	1194
104	120	80	24	98	N	N	4	thylparath	15			6	0	4	0			1	120	334	5	5			N			N	0	1	1	2	2	6	N	6011
84	300	60	28	92	Y	N	10	aunalpho	4		27/01/2014 27/01/2014	9	3	1	1	41666.00	41666.00	1	80	80			4		N			N	4	3	2	2	1	12	N	967
140	300	70	20	96	Y	N	9	zerofertfo	15			5	0	1	1	41683.00	41688.00	1	60	156	5	5			N			N	0	2	1	1	1	7	N	180
160	130	60	22	94	N	N	8	phosite	15			6	0	4	0			1	30	855					N			N	0	1	1	2	1	5	N	10357
160	120	80	28	94	N	N	1	chlorpyrif	12		20/03/2014 20/03/2014	7	0	4	0			1	60	210	5	5	12		N			N	0	1	2	1	6	N	9889
114	110	60	20	94	Y	Y	3	limethoat	13		13/03/2014 13/03/2014	6	0	1	2	41683.00	41684.00	1	180	390	4	4	13		N			N	4	2	2	2	1	5	N	7314
152	120	80	30	94	N	Y	1	chlorpyrif	15			6	0	4	0	41685.00	41700.00	1	60	275	5	5	14		Y	41697.00	41700.00	N	0	1	1	2	1	5	N	284
150	110	90	36	96	Y	Y	10	aunalpho	14			15	8	2	6	41685.00	41700.00	2	120	594	4	4	14		N			N	4	2	1	2	1	10	N	93
158	160	100	22	93	N	N	3	limethoat	15			3	0	4	0			1	30	140	5	5			N			N	0	1	1	2	2	6	N	9344
130	120	80	18	100	N	N	10	aunalphos	15	10		5	0	4	0			1	15	388	5	5			N			N	0	1	1	2	1	5	N	186
112	130	80	28		N	N	3	limethoat	8		05/03/2014 07/03/2014	19	5	2	4	41704.00	41707.00	1	60	833	3	3	8		Y	41707.00	41707.00	N	4	3	2	2	2	13	N	3457
148	120	70	30	95	Y	Y	5	micrototipol	15			6	0	1	2	41708.00	41731.00	1	60	148	4	4			Y	41726.00	41733.00	N	4	2	1	2	2	11	N	148
112	120	70	30	97	N	N	1	chlorpyrif	15			11	9	3	9	41725.00	41733.00	3	60	140	2	1			N			N	0	1	1	2	1	5	N	205
74	110	70	12	96	N	N	8	phosite	15			5	0	4	0			1	60	125	5	5			N			N	0	1	1	2	1	5	N	6653
72	130	80	24	94	Y	N	10	aunalpho	15			5	0	4	0			1		75	5	5			N			N	4	2	1	2	1	10	N	161
116	120	70	20	100	N	N	9	zerofertfo	15	10		5	2	4	0	41793.00	41747.00	1	120	400	5	5			N	41741.00	41747.00	N	4	2	1	1	1	5	N	101
104	120	80	24	94	Y	N	9	zerofertfo	15	10		17	9	2	8	41741.00	41742.00	1	60	2	4	4		7	Y	41741.00	41747.00	N	4	2	1	1	1	9	N	47
138	140	80	28		N	Y	11	triacaphos	3		13/04/2014 13/04/2014	8	3	2	5	41745.00	41749.00	1	90	200	4	4	12	2	Y	41748.00	41749.00	N	4	3	2	2	1	12	N	226
112	300	70	16	94	Y	N	9	zerofertfo	15		19/04/2014 20/04/2014	8	4	2	5	41745.00	41749.00	1	90	200	4	4			N	41748.00	41749.00	N	4	2	1	2	1	10	N	136
138	110	70	22	95	N	N	7	hendhoal	13			4	0	4	0			1	75	205	5	5			N			N	0	1	1	1	1	5	N	137
80	300	60	22	97	N	N	4	thylparat	15			3	0	4				1	90	300	5	5			N			N	0	1	1	2	1	5	N	2994
96	110	80	26	95	N	N	10	aunalpho	15			6	0	4	0			1	30	122	5	5			N			N	0	1	1	2	1	5	N	8939
140	90	60	26	93	N	N	1	chlorpyrif	15			8	0	4	0			1	150	219	5	5			N			N	0	1	1	2	1	5	N	57
100	120	80	12	99	N	N	9	zerofertfo	13			4	4	4	0			1		375	5	5	13		N			N	0	2	1	1	1	7	N	182
150	90	50	46	80	Y	N	9	zerofertfo	13		10/04/2014 10/04/2014	8	4	4	0			1	60	140					N			N	0	2	1	1	1	4	N	175
88	300	60	22	97	Y	N	5	micrototipol	15		28/04/2014 29/04/2014	27	18	2	15	41753.00	41708.00	1	60	730	3	3	4		Y	41756.00	41708.00	N	4	3	1	2	1	11	N	75
104	170	100	18	97	Y	N	11	Dichorvos	9			11	4	2	4	41757.00	41760.00	1	120	249	4	4	4		Y	41760.00	41760.00	N	4	3	2	2	2	13	N	74
126	110	80	34	95	Y	N	2	Dichorvos	9		30/04/2014 30/04/2014	5	2	1	1	41759.00	41760.00	1	30	133	4	4	9		N			N	4	3	2	2	1	13	N	237
133	120	90	22	91	N	N	1	chlorpyrif	15			5	0	4	0	41791.00	41759.00	1	360	23	5	5	15		N			N	0	1	1	2	1	5	N	63
140	140	90	18	96	Y	N	8	phosite	15		09/05/2014 10/05/2014	11	5	2	4	41767.00	41773.00	1		150	3	3		8t	Y	41769.00	41773.00	N	4	1	1	2	1	9	N	352
102	300	70	26	94	N	N	1	chlorpyrif	15			5	0	4	0			1		50	5	5	15		N			N	0	1	1	2	1	5		5486
130	160	80	42	92	N	N	5	micrototipol	15			9	0	4	0			1	30	367			13		N			N	0	2	1	2	2	7		52
74	90	60	24	96	N	N	8	phosite	15			6	0	4	0			1	150	750			15		N			N	0	2	1	2	1	6		248
70	300	60	26	64	N	N	0		9		12/05/2014 12/05/2014	4	0	4	0			1	60	18			9		N			N	0	3	2	1	1	7		5317
140	80	60	32	92	Y	Y	6		9		12/05/2014 12/05/2014	7	3	1	1	41771.00	41772.00	1	120	240	5	5	6		N			N	4	3	2	1	1	11		99
120	90	50	18	87	Y	Y	1	chlorpyrif	15			10	3	2	4	41771.00	41775.00	1	300	795	4	4	15		Y	41774.00	41775.00	N	4	3	2	1	1	11		92
120	120	70	32	78	Y	N	9	zerofertfo	9		17/05/2014 17/05/2014	8	3	1	3	41776.00	41778.00	1	60	460	4	4	9		N	41776.00	41778.00	N	4	3	2	2	1	12		5801
143	90	60	44	90	N	N	3	limethoat	11		22/05/2014 22/05/2014	20	14	3	9	41781.00	41788.00	1	30	300	2	2	11		Y	41783.00	41789.00	N	0	2	2	2	2	8		250
120	120	70	20	95	N	N	4	thylparat	15			5	0	4	0	41821.00	41824.00	1	120	230	5	5			N			N	0	1	1	2	2	6		8495
155	140	90	50	70	Y	N	8	phosite	4			7	5	1	1	41821.00	41824.00	1	240	375	3	3	4		N			N	4	3	2	2	1	12		165
112	110	80	20	98	N	N	1	chlorpyrif	15			3	0	4	0			1	30	72	5	5			N			N	0	1	1	2	1	5		6085
110	150	100	26	95	N	N	10	aunalpho	15			6	0	4	0			1	30	370	5	5			N			N	0	1	1	2	1	5		37
96	110	80	20	94	N	N	0	ct identifi	15			10	0	4	0			1	150	262	5	5	15		N			N	0	1	1	1	1	4		2036
110	130	90	20	92	Y	N	3	limethoat	15		03/06/2014 09/06/2014	7	0	1	2	41791.00	41801.00	1		80	4	4	13		N			N	4	3	2	2	1	12		2760
80	180	80	16		Y	Y	5	aunalpho	7		13/06/2014 13/06/2014	7	3	1	1	41833.00	41983.00	1		90	4	4	5		N			N	4	3	2	2	1	12		76
92	110	70	26	94	N	Y	7	thylparat	7		12/06/2014 13/06/2014	14	11	2	11	41832.00	41812.00	1	60	130	3	4	7	8t	Y	41825.00	41832.00	N	4	3	2	2	1	13	Y	94
72	110	70	28	96	Y	N	5	micrototipol	15			5	0	4				1	40	150	5	5			N			N	0	1	1	2	2	5	N	7447
136	150	80	26	96	N	N	0	phosite	15		22/06/2014 22/06/2014	8	5	2	5	41812.00	41817.00	1	120	205	3	3		9t	Y	41815.00	41817.00	N	4	3	1	2	1	10		208
70	120	80	22	99	N	N	5	micrototipol	15			6	0	4	0			1	90	295	5	5			N			N	0	2	1	2	1	6		223
124	300	70	36	77	N	N	10	aunalpho	6	10		7	2	1	2	41821.00	41822.00	1		210	4	4	15		N			N	4	3	2	2	1	12		215
105	110	70	24	96	Y	N	10	aunalphos	15	10		13	9	2	5	41822.00	41826.00	1	150	720	4	4			Y	41824.00	41826.00	N	4	3	2	2	1	12		48
112	300	70	22	94	N	N	11	triacaphos	15			14	5	3	5	41824.00	41829.00	1	45	100	3	3			Y	41824.00	41829.00	N	0	2	2	2	1	6		1375
62	110	60	24	96	N	N	1	chlorpyrif	15			6	0	4				1	120	210					N			N	0	2	2	2	1	6		1700
108	120	60	44	78	N	N	7	hendhoal	11		04/07/2014 04/07/2014	6	0	4				1	60	285			11		N			N	0	3	2	2	2	9		791
105	110	70	12	93	Y	N	3	limethoat	9		15/07/2014 15/07/2014	8	6	1	2	41815.00	41836.00	1	60	165	4	4	11		N			N	4	3	2	2	2	13		519
68	110	80	15		Y	N	8	phosite	3		24/07/2014 24/07/2014	4	2	1	1	41844.00	41844.00	1		120	4	4	3		N			N	4	3	1	2	1	8		10725
98	300	80	26	94	Y	N	8	phosite	2		16/07/2014 24/07/2014	26	11	2	11	41691.00	41660.00	1	120	710	2	2		2	Y	41655.00	41660.00	Y	4	3	1	2	1	12	N	54
70	120	80	30	96	Y	N	0		5		01/07/2014 12/07/2014	11	11	2	12	41821.00	41832.00	2		420	2	2		4	Y	41823.00	41832.00	Y	4	3	2	1	1	11	Y	205
70	110	80	12	45	Y	N	0		3		01/07/2014 12/07/2014	26	15	2	13	41640.00	41652.00	1		180	4	4	3	2	Y	41645.00	41652.00	Y	4	3	1	1	1	10	N	116
89	110	80	12		Y	N	11	triacaphos	11		07/12/2013 12/12/2013	46	22	2	20	41606.00	41625.00	1		60	2	2		2	Y	41609.00	41625.00	Y	4	3	2	2	1	12	N	175
70	60	30	30	93	Y	Y	3	limethoat	7		24/07/2014 25/06/2014	50	37	2	38	41814.00	41851.00	1		65	1	1	7		Y	41817.00	41851.00	N	4	3	2	2	1	13	Y	412
72	160	90	22	94	Y	N	6	Phenodil	12	2	01/08/2014 02/08/2014	11	10	2	10	41852.00	41861.00	1	60	1440	2	1		2	Y	41855.00	41861.00	N	4	3	2	1	1	11	Y	201
130	130	90	34	70	Y	N	0					4	2	2	4	41852.00	41855.00	2	60	365	2	2			Y	41855.00	41855.00	N	4	3	1	1	1		Y	1142
120	120	70	20	100	N	N	9	zerofertfo		10		5	2	4				1	120	400	5	5			N			N	0	1	1	1	1	4	N	100

THE END